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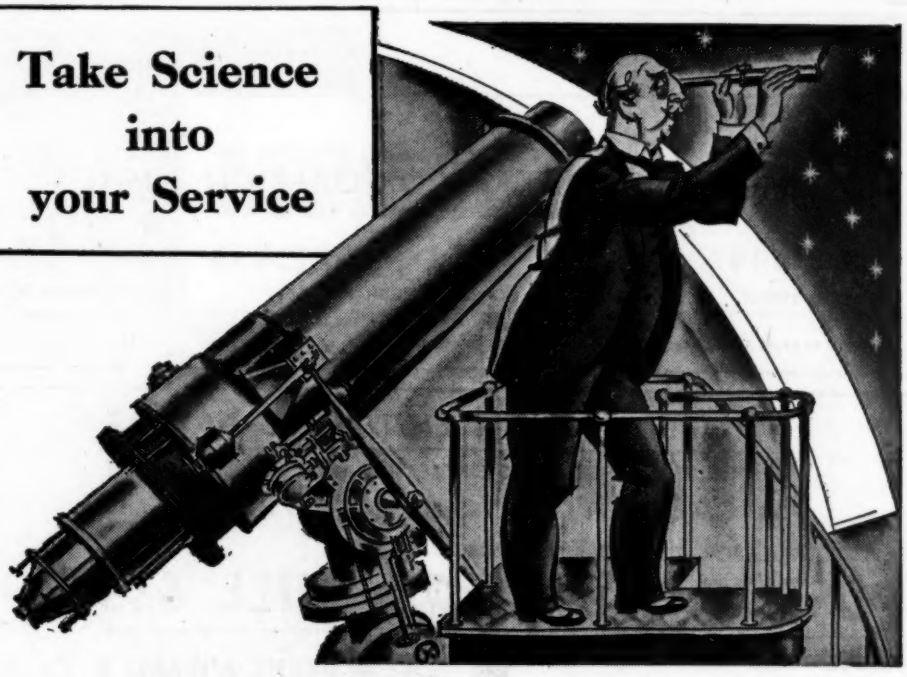

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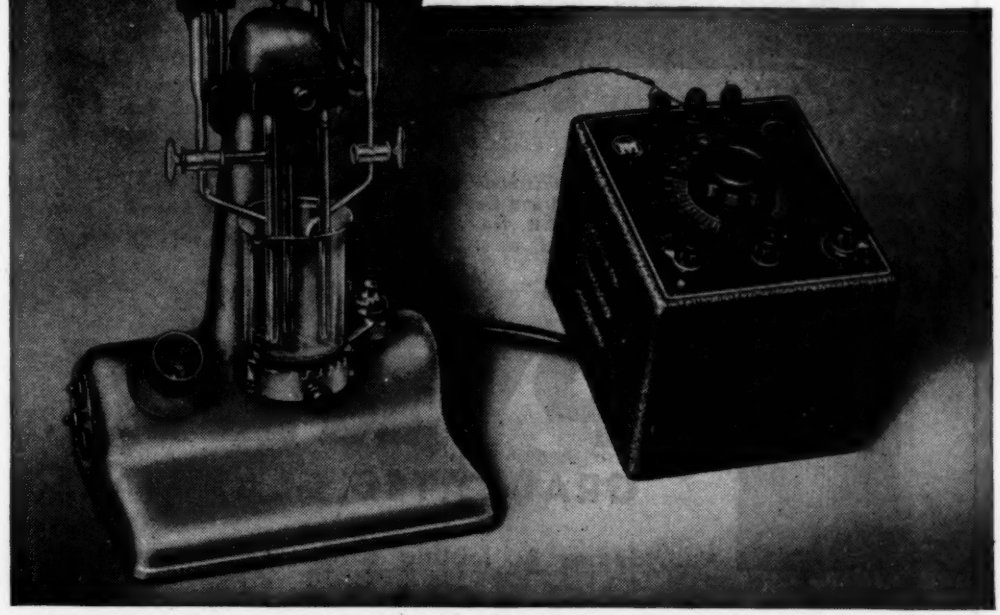

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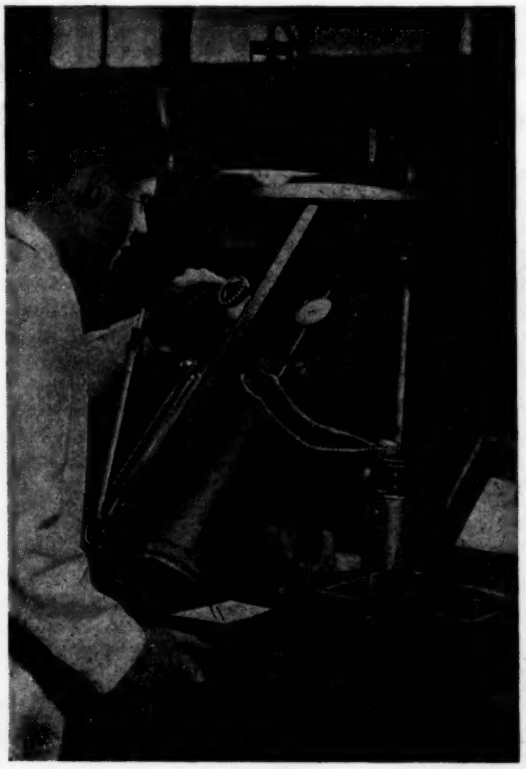

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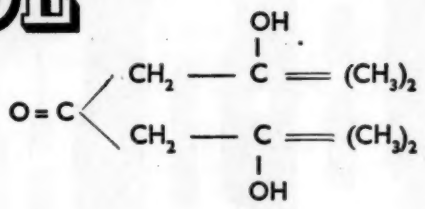

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110. *An Electrical Sorption Balance.*

By S. J. Gregg.

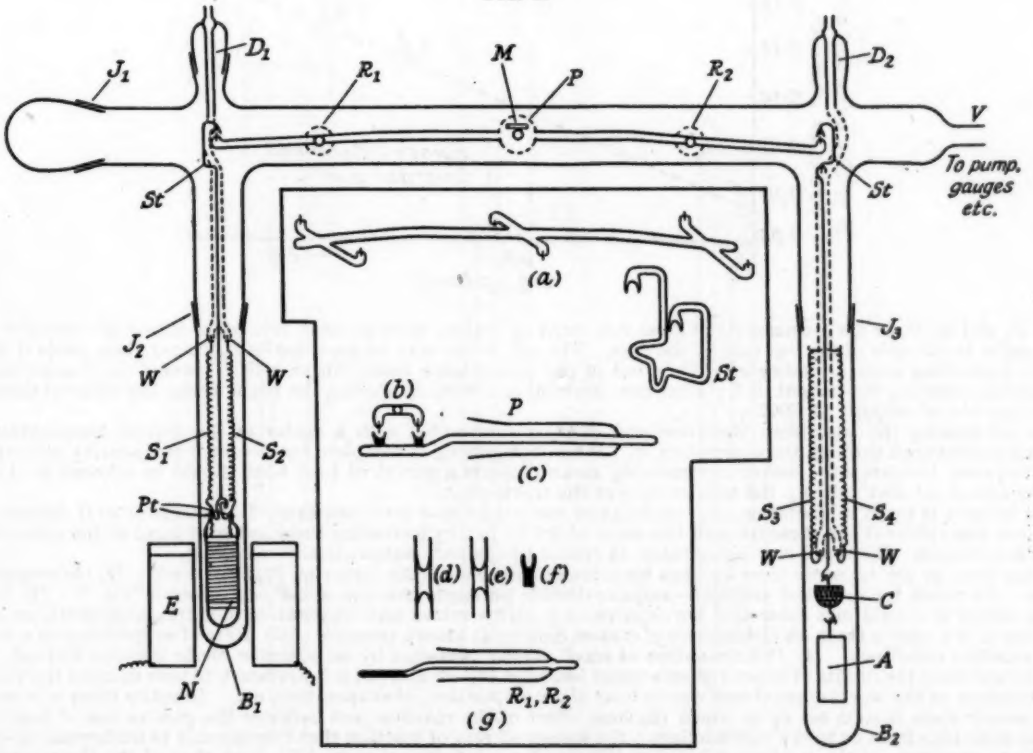
The sorption balance, which utilises an electromagnetic principle, has a sensitivity of *ca.* 0·0003 g., which is independent of the total load (10—20 g.). It is suitable for measuring adsorption, rate of decomposition, rate of evaporation, rate of effusion, etc. Its maximum range is about 0·4 g. of adsorbate.

The sorption balance here described has been designed to overcome the drawback, inherent in most existing designs, that a high sensitivity demands a low total load. Its sensitivity, which is of the order 0·0003 g., is independent of the total load, which may be of the order 10—20 g. The change in weight of the adsorbent due to uptake of adsorbate is measured by counterbalancing it electromagnetically. In principle it is similar to the instrument described by Blewett (*Rev. Sci. Instr.*, 1939, **10**, 231) in which an external solenoid interacts with a magnet attached to the balance arm, except that the magnet is replaced by a solenoid carrying a current, thereby eliminating any magnetic hysteresis effects. Anderson (*Trans. Faraday Soc.*, 1915, **11**, 69) used a very similar idea, having one solenoid hung from the arm of an ordinary balance, and two stationary solenoids; the balance was housed in a bell-jar which could be evacuated. This arrangement is not very convenient for out-gassing and similar operations, however, and not suitable for high-vacuum work.

Experimental.

In the present model the deflection of the balance arm is followed by an optical lever, and the arm is brought back to an arbitrary zero by adjusting the currents in " exterior " solenoid E and if necessary in " interior " solenoid N (Fig. 1); the force exerted between E and N is proportional to the product of the currents they carry. The balance can be

Fig. 1.



calibrated by hanging known weights on the right-hand side, and measuring the external and the internal current, $I_{ext.}$ and $I_{int.}$, when the arm has been brought back to its zero position. Small changes in weight can be followed by the scale deflection, a separate calibration for weight versus scale deflection having been carried out.

The balance beam is of Pyrex tubing (*ca.* 5 mm. in diameter) with small side tubes sealed on and then cut off short, forming sleeves which accommodate cut-off sewing needles serving as bearings (Fig. 1*a*). There are two such needles in the middle and two at each end; they bear on hemispherical depressions in glass, made by sinking in a piece of Pyrex tubing, about 4 mm. in diameter, near one end [Fig. 1(*d*)], then blowing gently [Fig. 1(*e*)], and finally cutting off [Fig. 1(*f*)]. The main glass bearings, *i.e.*, those for engaging the two middle needles, are fused on to a glass support P which is joined on to a standard ground glass joint by an internal seal [Figs. 1, 1(*b*), 1(*c*)]. Small glass stirrups *St* are provided at each end of the beam to accommodate the glass suspension rods which carry the loads [Figs. 1 and 1(*a*)].

The needles are fitted into their sleeves by means of vacuum wax or Wood's metal; by gently moving the arm and the glass bearings relatively to one another whilst the cementing material is still warm (before erecting the balance) it is possible to " feel " the position of minimum potential energy of the needle points with relation to the glass hemispheres;

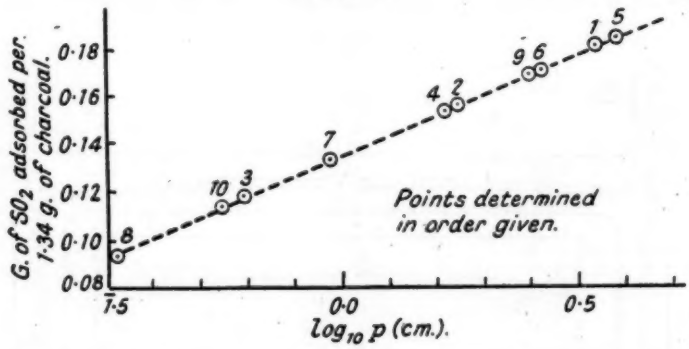
they are then held in this position till the cement solidifies. This procedure ensures that in use the needle points shall always return to the same zero position after adventitious displacements due to jarring. A galvanometer mirror M is mounted at the centre of the beam and reflects a spot of light on to a scale. The sensitivity of the balance is fixed, by trial and error, by suitable bending of the arm in the flame before erection. The balance is then mounted in a "case" of Pyrex tubing about 40 mm. in diameter with No. B34 standard ground glass joints at J_1, J_2, and J_3 (Fig. 1).

The inner solenoid N, of 1000 turns of 36 S.W.G. silk-covered copper wire, is enclosed in a soda-glass container provided with a hook at the top, the two leads being taken through platinum seals (Fig. 1). To conduct the current into the solenoid from the outside of the balance case, two springs S_1 and S_2 of fine wire are used. In the present model each spring consists of 80 turns of 42 S.W.G. copper wire, the turns being about 4 mm. in diameter; platinum wire can be used, but the maximum permissible current is thereby reduced. An identical pair of springs (S_3 and S_4) is attached to the other arm and mounted in such a sense that the two sets mutually compensate, in that both of the sets stretch together and both contract together. This compensating device ensures that the springs shall not appreciably reduce the sensitivity of the balance or introduce excessive damping. The compensation springs can be used as leads to a resistance thermometer incorporated in the adsorbent container, when it is desired to measure heats of adsorption (see next paper); when not so used, they may be connected in series with the solenoid springs S_1 and S_2, thereby compensating any effect on the elasticity of these springs due to the heating effect of the small current, *ca.* 0·05 amp., which they carry. Connection from the four springs through the balance case is made by mercury–tungsten seals W (platinum seals through Pyrex glass are not vacuum-tight) attached to the lead-in tubes D_1 and D_2 which accommodate copper leads.

The outer solenoid E is 1000 turns of 22 S.W.G. copper wire, and will carry a maximum current of about 1·2 amp. without overheating.

In addition to the adsorbent container hung from the right-hand arm, there is a counterpoise C; a small sealed bulb containing mercury, or a small glass bucket which can be charged with lead shot, is suitable. The weight of the counterpoise is such that the balance beam can, at the commencement of the experiment, be brought to its zero position by a very small current in the outer solenoid. The container is hung on to the counterpoise by means of a small glass hook on the latter.

FIG. 2.



At R_1 and R_2 there are arrestments of glass rod, fixed by sealing through small side tubes joined horizontally and at right angles to the axis of the top tube of the case. The side tubes may be provided with ground glass joints if desired, thereby permitting some adjustment. When not in use, the balance beam can be gently lowered on to arrestment R_1 by gradually altering the current in E; after thus lowering and then re-floating the beam again, the value of the weight can be reproduced within $\pm$0·0002 g.

For out-gassing the adsorbent, the lower end of B_2 is surrounded with a heater at the desired temperature, and pumping commenced through the connection V. When out-gassing is complete the heater is replaced by a thermostat at the required temperature; before commencing measurements a period of ½—1 hour should be allowed to elapse so that the adsorbent may take up the temperature of the thermostat.

The balance is rapid in operation, and readings of the weight may be taken every 15 seconds or so if desired. The maximum adsorption it can measure is of the order of 0·4 g., but by increasing the number of turns in the solenoids this could be increased. Steps are now being taken to render the balance automatically recording.

It has been in use for some time and has been found suitable for the following types of work: (1) Adsorption isotherms: the result for a typical example—sulphur dioxide on sugar charcoal at 25°—is shown in Fig. 2. (2) Rate of decomposition of a solid in a controlled atmosphere—*e.g.*, dehydration and rehydration of a crystal hydrate, or decomcomposition of a carbonate in an atmosphere of carbon dioxide at known pressure. (3) Rate of evaporation in a vacuum of a crystalline substance. (4) Determination of small vapour pressures by an adaption of the effusion method.

In interpreting the results of measurements under headings (2), (3) and (4), it is necessary to bear in mind the variation in temperature of the working substance due to heat of decomposition, of evaporation, etc. In many cases it is probable that a steady state is soon set up in which the heat effect of the reaction just balances the gain or loss of heat by the working substance from or to the surroundings; the measured rate of reaction then corresponds to isothermal conditions with the temperature of the working substance differing by a definite amount, $\Delta T°$, from that of the thermostat. In favourable cases it is possible to make a reasonably good estimate of $\Delta T°$. In ordinary adsorption work, however, where a charge of gas is suddenly admitted to or withdrawn from the adsorbent, the temperature of the latter may rapidly change by several degrees (see next paper); the balance still accurately measures the rate of adsorption, but it is not an isothermal rate.

WASHINGTON SINGER LABORATORIES, UNIVERSITY COLLEGE, EXETER. [*Received, December 29th*, 1945.]

111. *An Electrical Sorption Balance and Calorimeter.*

By S. J. Gregg.

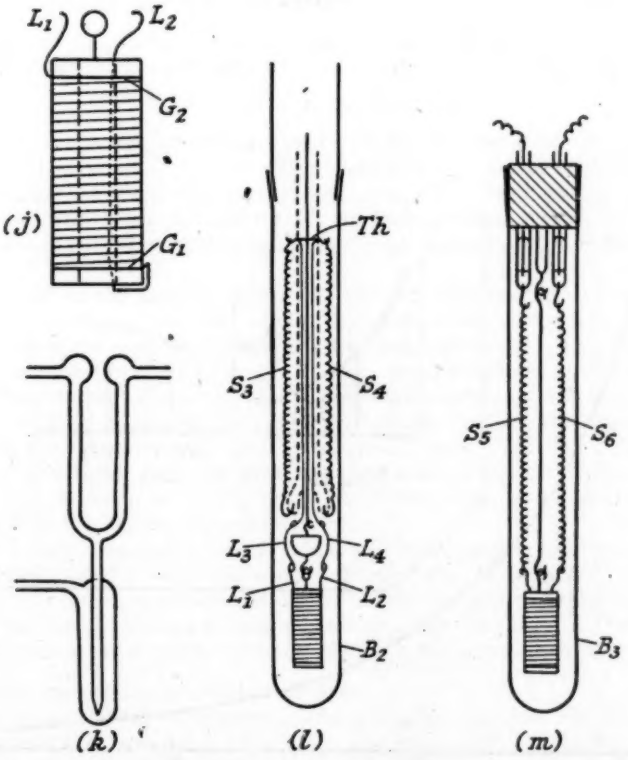
This apparatus enables the differential heat of adsorption to be determined simultaneously with measurements of the adsorption itself provided the pressure of the gas is greater than about 1 mm. of mercury. Its performance has been tested by measurements of the differential heat of adsorption of water vapour on "active alumina": the results agree satisfactorily with those calculated from the adsorption isotherms by means of the Clausius–Clapeyron equation, and from heat-of-wetting measurements. For the adsorption range 0·10—0·20 g. of water vapour per g. of alumina, the differential heat of adsorption lies within 5% of the latent heat of condensation.

The usefulness of the sorption balance technique would be considerably enhanced if the heat of adsorption could be measured at the same time as the adsorption itself. By incorporating a thermometric device into the sorption balance described in the foregoing paper, it has been found possible to measure the temperature rise brought about by adsorption; since the amount of adsorption causing this heat evolution is also measured, by the sorption balance, the differential heat of adsorption can be calculated once the heat capacity of the adsorbent and its container, and also the magnitude of the cooling losses, are known.

Experimental.

To adapt the sorption balance in this way, the adsorbent container is made of copper or silver foil (approx. 0·1 mm. thick) bent into a cylinder of approx. 12 mm. diameter and 40 mm. length, and soldered down the seam. Co-axial

Fig. 1.



with it is a cylinder of copper or silver gauze small enough in mesh to retain the particles of adsorbent, of the same length but about 6 mm. in diameter. The two cylinders are fastened together by soldering to a ring of foil, serving as the bottom of the container. The space between the two cylinders is destined to receive the adsorbent, the inner cylinder of gauze facilitating the access of gas to the adsorbent [Fig. 1(*j*)]. The outer cylinder is wrapped in a piece of mica cleaved as thinly as possible, the mica being fastened top and bottom by binding with rings of copper or silver wire soldered in position. The resistance thermometer wire is then wound round the outside of the mica cylinder commencing by soldering it on to one ring [G_1, say, of Fig. 1(*j*)] and winding the turns as closely as possible without touching, finishing off at G_2 where it is again fastened by soldering. The wire should be of material with a high temperature coefficient of resistance: 40 S.W.G. nickel or platinum is suitable.

The container *A*, when charged with a known weight of adsorbent, is hung from the right-hand arm of the balance (see Fig. 1 of previous paper), the counterpoise *C* being adjusted in weight as described in the previous paper. The balance, together with the connecting tubes and manometers, storage reservoir for the adsorbate vapour, etc., must be surrounded by an air thermostat kept constant to within ¼°. The electrical leads L_1 and L_2 from the container are soldered on to the bottom of leads L_3 and L_4, and the outer tube B_2 placed in position. The external leads connected

to L_3 and L_4 are then taken off to one arm of a Callendar–Griffiths bridge (*Phil. Trans.*, 1891, **182** *A*, 43, 119) or a suitable modification thereof. Another container as similar as possible to A but with a winding of some 10% lower resistance, and having springs S_5 and S_6 exactly similar to S_3 and S_4 for connecting the winding to the exterior, is set up in tube B_3 [Fig. 1(*m*)]. This arrangement serves as the compensation resistance and is connected into the " compensation " arm of the bridge. In operation, B_3 is placed alongside the working tube B_2 in the thermostat.

The resistance thermometer is calibrated for temperature by leaving B_3 and B_2 in the same thermostat at temperature T_1 (say 20°) for an hour or so to come into thermal equilibrium, and taking the bridge reading—say z_1 ohms. B_2 is then transferred to a thermostat at T_2 (say 40°) and the new resistance (say z_2) read off after another hour or so. The calibration figure is then $(z_2 - z_1)/(T_2 - T_1)$ ohms per degree.

To carry out an experiment, the adsorbent is first out-gassed by pumping through V (see Fig. 1 of foregoing paper) and the tube T_2 is then surrounded by a water thermostat at the desired temperature. After about an hour the first admission of gas is made. This is best done by means of a mercury valve [Fig. 1(*k*)] which can be operated by a two-way tap on the control table so that readings on the bridge and on the sorption balance scale can commence immediately afterwards. Readings of both θ and Δw are taken at frequent intervals so as to permit the plotting of accurate curves of θ versus time, and of Δw versus time, or better versus log time (Δw g. = increment in weight adsorbed after the particular admission of gas; θ = increase in temperature above the commencing temperature).

The response of the resistance thermometer is very rapid, as reference to Fig. 2, which gives the θ–t curve for an admission of water vapour to active alumina, will show (full line). This rapid response arises both because most of the adsorbent is in contact with the metal of the conductor, and also because the adsorbent, though a bad conductor, is at nearly the same temperature throughout since the process of adsorption (particularly with a granular adsorbent) occurs almost uniformly throughout the adsorbent. Actually, there must be a small temperature gradient from the middle of the adsorbent layer to its sides because the material of the calorimeter container does not participate in the adsorption and so must receive its heat only from the adsorbent.

Calculation of the Differential Heat of Adsorption, ΔH.—θ is first corrected for loss of heat to the surroundings by an application of Newton's law of cooling in the ordinary manner. (The system has been found to obey

FIG. 2.

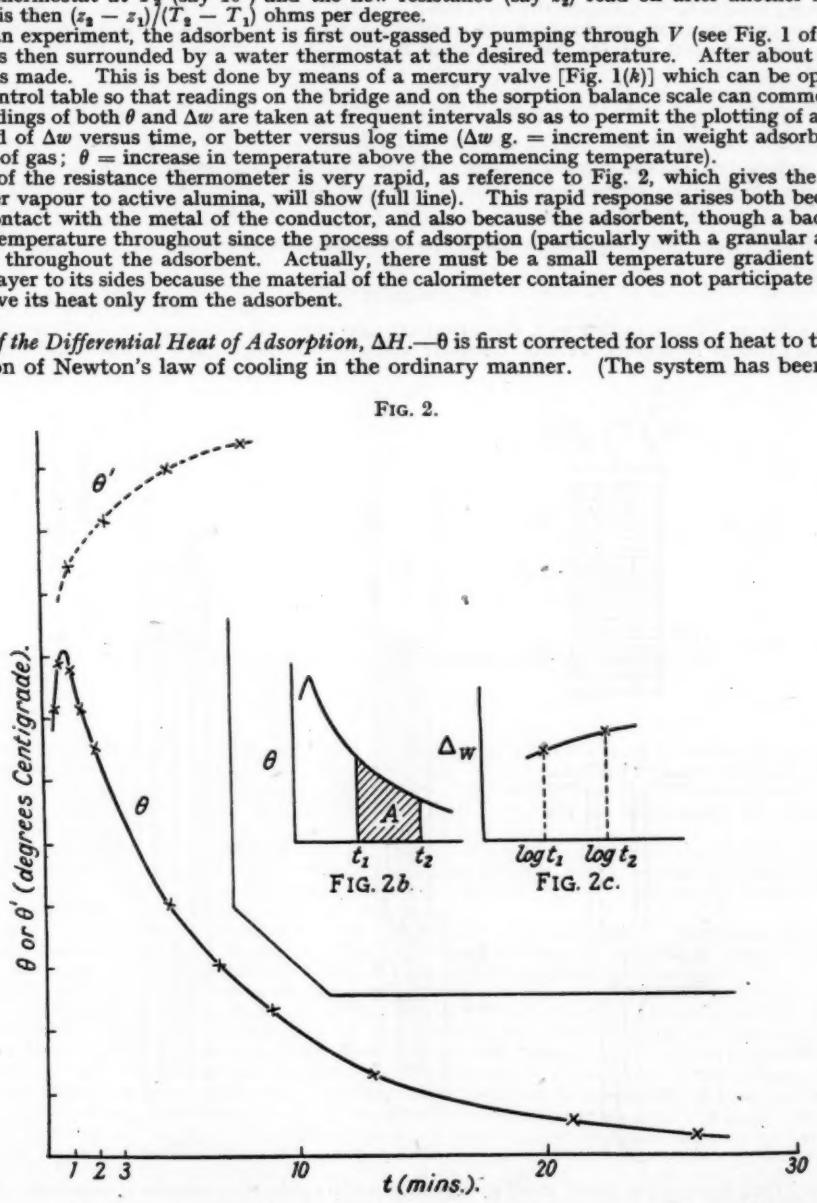


FIG. 2b. FIG. 2c.

this law with reasonable accuracy.) The time axis is divided into short intervals of the order 1—2 minutes; the total area under the curve up to any time t, when multiplied by the Newton constant k (determined as described later), gives the loss of temperature due to cooling effects; adding to the ordinate at t, one obtains θ', the corrected temperature. A typical θ' curve is shown in Fig. 2 (broken line) together with its corresponding θ curve (full line).

The differential heat of adsorption is then given by

$$\Delta H = \frac{\theta' \text{ at time } t}{\Delta w \text{ at time } t} \times C \times M \text{ cals. per mole of adsorbate,}$$

where M is the molecular weight of the adsorbate and C calories is the thermal capacity of the container and

contents. It is clear that a number of values of ΔH can be obtained from each θ–t curve, depending on the number of time intervals chosen.

Determination of the Cooling Constant k *and the Thermal Capacity* C.—The *amount* of heat lost to the surroundings per second is a function of the size, shape, and material of the surface of the cooling body, the conductivity of the surrounding gas, and the temperature difference θ, but not of the mass of the body. This amount of heat is given by $C \cdot d\theta/dt = Ck\theta$, *i.e.*, Ck cals. per second for unit temperature difference. The product Ck should therefore be a constant for a given container under given conditions, independently of the individual values of C; Ck will, of course, depend on the thermal conductivity of the gas, and so will vary from gas to gas. The determination of Ck, described below, must accordingly be carried out separately for each gas used in the calorimeter. Ck is independent of the *pressure* of the gas, however, provided this is in excess of the figure for which thermal conductivity begins to depend on pressure, *i.e.*, about 1 mm. of mercury in the present experiments.

To determine Ck, the winding of the resistance thermometer (Th) is used as a heating coil; Th is disconnected from the bridge by means of a two-way switch and a known current passed through it for about 2 hours till thermal equilibrium is reached; the pressure of the gas must be above the critical figure referred to above. At a given moment, the switch is turned over so as to disconnect Th from the heating current and connect it to the bridge. Readings of θ are taken at frequent intervals. Except for the first few seconds, these readings closely obey Newton's law: by plotting log θ against time a good straight line is obtained. Extrapolating back to the moment when the heating current was switched off gives a temperature θ''. We then have:

$$\text{Loss of heat to the surroundings per sec.} = Ck\theta''$$
$$\text{Net gain of heat from the current per sec.} = (I^2 - I_0^2)\omega/J$$

where I is the heating current, I_0 the current passing through Th when connected to the bridge, ω the resistance of Th, and J the mechanical equivalent of heat. Consequently

$$Ck = (I^2 - I_0^2)\omega/J\theta = P \text{ (say)}$$

so that Ck can be obtained. The corresponding value of k can be obtained as 2·3 × slope of the curve of $\log_{10}\theta$ versus time; C is then given as $C = P/k$. This method for C has been checked by experiments with a substance of known specific heat—calcite—in the container. The mean of the results (1·32 cals.) agreed satisfactorily with the value (1·28 cals.) calculated from the known thermal capacity of the container and the specific heat and mass of the calcite (capacity of container by ice calorimeter = 0·485 cal.; capacity of 4·11 g. of calcite = 0·795).

C is, of course, a function of the amount adsorbed, so that, assuming the specific heat of the adsorbed material is constant—say c—the heat capacity C for any given total adsorption w grams is $C = C_0 + wc$, where C_0 is the heat capacity of the container plus the out-gassed adsorbent. An estimate of c can be obtained by carrying through a determination of Ck, and thus of C, on the adsorbent charged with several different contents of adsorbate. This has been done for water vapour on alumina, and the specific heat c of the adsorbed water found to be 1·10 ± 0·15, in moderate agreement with Porter and Swain's figure of 0·93 for the specific heat of water adsorbed on sugar charcoal (*J. Amer. Chem. Soc.*, 1933, **55**, 2792). The margin of error is considerable, but it should be noted that the total heat capacity of the water rarely amounts to 25% of the total heat capacity C, so that even an error of ±15% in c leads at the worst to an error of ±4% in C. Actually, the figure $c = 1{\cdot}0$ was used in the subsequent calculations.

Determination of the Cooling Constant k.—The value of k corresponding to any given adsorption can be calculated from the relation $k = P/C = P/(C_0 + wc)$. It can also be obtained "internally" from the θ–t and the Δw–log t curve for any given admission of gas, as follows: select two times t_1 and t_2 where the adsorption has become nearly constant so that the θ–t curve is *nearly* of Newton form. The actual cooling is then the Newton cooling effect less the heating effect of the additional adsorption $(w_2 - w_1)$. Then

Heat loss between t_1 and t_2 due to Newton cooling
$= Ck \times$ Area under the curve between t_1 and $t_2 = CkA$, say (see Fig. 2*b*).
Heat gained by adsorption between t_1 and $t_2 = (w_2 - w_1)\Delta H/M$ (cf. Fig. 2*c*)
Thus
Net heat lost between t_1 and $t_2 = CkA - (w_2 - w_1)\Delta H/M$
so that fall of temperature between t_1 and t_2

$$= \theta_2 - \theta_1 = \frac{CkA - (w_2 - w_1)\Delta H/M}{C}$$

i.e.,

$$k = \frac{\theta_2 - \theta_1}{A} + \frac{(w_2 - w_1)\Delta H/M}{CA}$$

All quantities on the right-hand side of this last equation can be obtained from the two curves except ΔH and C. Since these appear in the second term, which is small compared with the first, approximate values may be used for them. A check on these k values is to see whether the product Ck (C being calculated by equation $C = C_0 + wc$) gives a constant independent of w. In practice the deviation of Ck from constancy is

sometimes considerable—up to 15%—so it is best to calculate k as P/C and use the " internal " method as a general check.

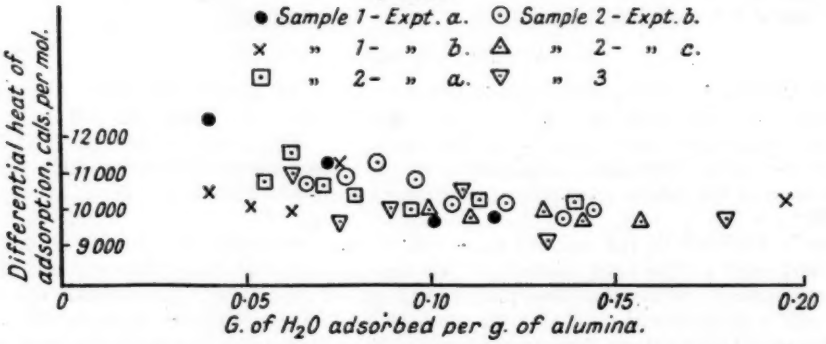
Failure of the Calorimeter at Low Pressures.—The variation of k with pressure in the low-pressure range, already referred to, is great enough to render the calorimeter unreliable at pressures below about 1 mm. of mercury. It is convenient to note that the Pirani gauge, since it is based on the pressure-dependence of thermal conductivity, begins to function at approximately the pressure where the calorimeter begins to fail. In addition, the breakdown is signalised by the fact that the equilibrium reading on the Callendar–Griffiths bridge (*i.e.*, the reading when adsorption has become constant so that the bridge current heating effect is just balanced against cooling losses) is no longer constant but depends upon the pressure.

Application to Desorption.—The procedure so far described for the heating effect accompanying adsorption, is equally applicable to the cooling effect of desorption.

Illustrative Results from the System Alumina–Water.—The measurements here recorded are restricted to the pressure range 0·1—0·7 of the saturated vapour pressure of water at 25° and 35°, and the adsorption range 0·05—0·18 g. of water vapour per g. of alumina. The alumina was out-gassed for one hour at 110°.

In Fig. 3, values of the differential heat of adsorption ΔH are plotted against the adsorption. It will be seen that the values of ΔH fluctuate somewhat irregularly around a value of 10,300 cals. per mole, with a maximum deviation of some $\pm$1000 cals. and an average deviation of about $\pm$400 cals. ΔH appears to fall slightly with increasing adsorption. The fluctuations are no doubt largely due to experimental error (particularly in assessing the cooling effect) but may perhaps also be attributed in part to the fact that the adsorption is not carried out under strictly reversible conditions so that a proportion of the " external work " RT (= *ca.* 600 cals. per mole) fails to register as heat in the calorimeter. This proportion would vary from measurement to measurement and might perhaps account for 100 or so cals. per mole out of the total fluctuation.

FIG. 3.


● Sample 1 - Expt. a. ⊙ Sample 2 - Expt. b.
× " 1- " b. △ " 2- " c.
⊡ " 2- " a. ▽ " 3
Differential heat of adsorption, cals. per mol.
12 000
11 000
10 000
9 000
0
0·05
0·10
0·15
0·20
G. of H2O adsorbed per g. of alumina.

These directly determined values of ΔH may be compared with the indirect value obtained by two different methods, (i) application of the Clausius–Clapeyron equation to isotherms at neighbouring temperatures; (ii) determination of the heating of wetting in liquid water of alumina samples charged to different contents of water vapour.

Method (i). Using the sorption balance, desorption isotherms were measured at 18°, 25°, and 35° respectively (desorption isotherms are known to approximate more closely to equilibrium values then adsorption isotherms); the alumina was out-gassed as already described, exposed at 25° to nearly saturated water vapour, then desorbed in steps. When the adsorption had fallen below the range under investigation, the thermostat was changed to 35°, the alumina again charged with nearly saturated water vapour, and the desorption curve mapped out at this temperature. The procedure was then repeated at 18°.

The differential (" isosteric ") heat of adsorption at any given adsorption w is then given by the integrated form of the Clausius–Clapeyron equation :

$$\Delta H = 2{\cdot}303\, RT_1T_2\,(\log_{10}p_2 - \log_{10}p_1)/(T_2 - T_1) \text{ cals. per mole of absordate.}$$

Strictly, the equation is only applicable if the adsorption is reversible with respect to temperature : on raising the temperature, *e.g.*, from 25° and 35°, under constant volume conditions, a point on the 35° isotherm should be obtained; by cooling to 25° one should return to the starting point. On trying a few such temperature jumps on the present system, this exact return was not always achieved, showing the system to be incompletely reversible with respect to temperature. The lack of reversibility is related to the hysteresis loops which were found in the adsorption isotherms in some other experiments not recorded here. Consequently, the ΔH values given below cannot be regarded as more than approximate—an inference emphasised by the imperfect agreement amongst the values themselves :

Isotherms.	G. H_2O per g. of alumina.	ΔH, cals. per mole of H_2O.	Isotherms.	G. H_2O per g. of alumina.	ΔH, cals. per mole of H_2O.
25° and 35°	0·165	10,100	18° and 25°	0·170	11,000
	0·140	10,500		0·145	11,300
	0·120	12,100		0·120	11,700

For the most part, these values are rather higher than those from the electrical sorption calorimeter; the discrepancy is no greater, however, than that usually found between calorimetric and isosteric values of the heat of adsorption (cf. Brunauer, "Physical Adsorption of Gases and Vapours," 1943, 223—225); it is probably to be accounted for partly by the RT term and partly by the lack of reversibility.

Method (ii). A number of weighed samples of the alumina were placed in bulbs and fused on to an attachment whereby they could be evacuated simultaneously. After an hour's out-gassing at 110°, the adsorbent was exposed to saturated water vapour in the absence of air. After some hours (adsorption equilibration is very slow near the saturated vapour pressure) the attachment was weighed, one bulb sealed off, and the attachment reweighed; next, some water vapour was pumped out, the weighing and sealing-off was repeated, and so on for all the bulbs. By simple arithmetic, the weight of water adsorbed in each bulb can be calculated. The heat of wetting of the contents of each bulb was then determined by breaking it under water in a thaw-melt calorimeter at 19·0° (acetophenone as the calorimeter working substance). By plotting the heat of wetting per g. of alumina against the weight of water vapour adsorbed per g. of alumina, an approximately straight line is obtained the slope of which, by application of Hess's law, can be shown equal to the "net heat of adsorption," *viz.*, $(\Delta H - L)$, where L is the latent heat of condensation of water at 19° (cf. Lamb and Coolidge, *J. Amer. Chem. Soc.*, 1920, **42**, 1146). Successive experiments with three or four bulbs in each experiment gave the following results for $(\Delta H - L)$: 250, 100, 300, 380, 500 cals. per mole of water vapour. The differences, which exceed the error of measurement, are probably due to the lack of adsorption equilibrium in the vapour-charged samples —the same kind of error as that discussed under method (i). Since L is 10,530 cals. per mole (International Critical Tables, **5**, 148) this gives for ΔH at 19° values ranging from 10,630 to 11,030 cals. per mole. These are somewhat higher than the results from the sorption calorimeter, but having regard to the uncertainty as to the RT term in the latter and as to equilibration in the former, the agreement between the two methods can be regarded as satisfactory.

Thus, the results from methods (i) and (ii) may be considered as evidence for the satisfactory performance of the electrical sorption calorimeter. Summarising the results from all three methods, one may say that under reversible conditions, the differential heat of adsorption ΔH of water vapour on alumina lies within 5% of the latent heat of condensation for the pressure range 0·1—0·7 of the saturated vapour pressure, and the approximate adsorption range 0·10—0·20 g. of water per g. of alumina; ΔH is nearly independent of the amount adsorbed, over this range.

The calorimeter should be suitable for measuring isothermal heats of reaction of gases with solids, isothermal heats of decomposition of solids, etc.

The author thanks Mr. K. Sing, B.Sc., for carrying out most of the heat-of-wetting measurements, and Prof. F. H. Newman for the loan of a Callendar–Griffiths bridge. The sample of active alumina was kindly provided by Messrs. Peter Spence and Co.

WASHINGTON SINGER LABORATORIES, UNIVERSITY COLLEGE, EXETER. [*Received, December 29th*, 1945.]

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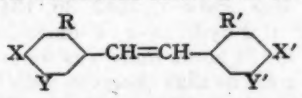
112. *Attempts to find New Chemotherapeutic Amidines. Part III.* Nuclear Substituted Derivatives of 4 : 4′- and 3 : 3′-Diamidinostilbene.*

By J. N. ASHLEY and J. O. HARRIS.

Syntheses of 2-*amino*-4 : 4′-*diamidinostilbene*, and the *dihydrochlorides of* 2-acetamido-, -chloro-, -bromo-, -iodo-, -hydroxy-, and -methoxy-4 : 4′-diamidinostilbene, and of 6 : 6′-dihydroxy-3 : 3′-diamidinostilbene, are described. The halogenated and monohydroxy compounds show greater trypanocidal activity than 4 : 4′-diamidinostilbene ("Stilbamidine"). The methoxy derivative is approximately as active, whilst the remainder are less active than Stilbamidine.

THE preparation and trypanocidal activity of a number of aromatic diamidines were described by Ashley *et al.* (*J.*, 1942, 103) and it was suggested there that the effect of nuclear substitution might be examined. The present communication describes a number of stilbene derivatives of the type



where R = Y = Y′ = H, X = X′ = NH_2·C(:NH), and R′ = NH_2, NHAc, Cl, Br, I, OH, and OMe, and also where X = X′ = H, R = R′ = OH, and Y = Y′ = C(:NH)·NH_2.

The results of the biological testing of these compounds will be reported in detail elsewhere, but it can be stated here that presence of a halogen atom or hydroxy group in 4 : 4′-diamidinostilbene increases, while presence of a methoxy, amino, or acetamido group decreases, the trypanocidal activity. 6 : 6′-Dihydroxy-3 : 3′-diamidinostilbene is less active than Stilbamidine, and is not curative.

Nuclear substitution appears to have no effect on antimalarial activity, but introduction of halogen slightly increases the antibacterial activity.

* The papers by Ashley, Barber, Ewins, Newbery, and Self (*J.*, 1942, 103) and Barber and Stickings (*J.*, 1945, 167) are to be regarded as Parts I and II respectively of this series.

The starting material for all the monosubstituted diamidines was 2-*nitro*-4 : 4′-*dicyanostilbene*. On one occasion only this was obtained from the Sandmeyer reaction on 2-*nitro*-4 : 4′-*diaminostilbene* which was readily prepared by the series of reactions. Condensation of 2 : 4-dinitrotoluene with 4-acetamidobenzaldehyde (Ashley *et al.*, *J.*, 1942, 113) gave 2 : 4-dinitro-4′-acetamidostilbene, previously prepared by Ruggli and Dinger (*Helv. Chim. Acta*, 1941, **24**, 173) by acetylation of the dinitroamine obtained by reduction of 2 : 4 : 4′-trinitrostilbene with alcoholic ammonium sulphide. The m. p. of our product was considerably higher than that recorded by these workers. Reduction of 2 : 4-dinitro-4′-acetamidostilbene with alcoholic ammonium sulphide yielded 2-*nitro*-4-*amino*-4′-*acetamidostilbene*, which on hydrolysis gave 2-nitro-4 : 4′-diaminostilbene. All other attempts to prepare 2-nitro-4 : 4′-dicyanostilbene by this method failed, as the complex obtained from the Sandmeyer reaction decomposed with almost explosive violence when it was heated in a vacuum according to the method previously described (Ashley *et al.*, *J.*, 1942, 111). Subsequently 2-nitro-4 : 4′-dicyanostilbene was prepared by condensation of 2-nitro-4-cyanotoluene (Banse, *Ber.*, 1894, **27**, 2161; Soderman and Johnson, *J. Amer. Chem. Soc.*, 1925, **47**, 1392) with 4-cyanobenzaldehyde (Ashley *et al.*, *J.*, 1942, 115) in presence of piperidine. Attempts to effect condensation in alcoholic solution or with acetic anhydride as condensing agent were unsuccessful.

Reduction to 2-*amino*-4 : 4′-*dicyanostilbene* was accomplished by heating with stannous chloride in a mixture of glacial acetic and hydrochloric acids. Conversion to the iminoether hydrochloride and 2-*amino*-4 : 4′-*diamidinostilbene* was accomplished by the usual methods. 2-Acetamido-4 : 4′-diamidinostilbene, isolated as the *dihydrochloride*, was similarly prepared from 2-*acetamido*-4 : 4′-*dicyanostilbene*.

2-*Chloro*-4 : 4′-*dicyanostilbene* was obtained from the corresponding amine by the Gatterman diazo reaction. The diazonium chloride was decomposed in boiling 15% hydrochloric acid in presence of copper bronze; with more dilute acid a by-product giving fluorescent solutions was formed which was removed only with difficulty. Decomposition of the diazonium sulphate with cuprous bromide gave only a 9% yield of 2-*bromo*-4 : 4′-*dicyanostilbene*, but this was increased considerably by diazotisation in 51% hydrobromic acid and subsequent decomposition in presence of copper bronze and boiling 12% hydrobromic acid. Decomposition in presence of more dilute acid favoured formation of the above, or a similar, fluorescent by-product whilst 51% acid caused hydrolysis of the cyano groups.

2-*Iodo*-4 : 4′-*dicyanostilbene* was prepared from the diazonium sulphate by treatment with aqueous potassium iodide.

The above three dicyano compounds were converted into 2-chloro-, 2-bromo-, and 2-iodo-4 : 4′-diamidinostilbene (all isolated as *dihydrochlorides*) by the usual method.

In view of the increased therapeutic ratios shown by the halogenated diamidines (I > Br > Cl) an attempt was next made to synthesise 2 : 2′-dibromo (or iodo)-4 : 4′-diamidinostilbene. The required 2 : 2′-*dinitro*-4 : 4′-*dicyanostilbene* was obtained in 11% yield by oxidation of 2-nitro-4-cyanotoluene with alcoholic sodium hypochlorite (cf. Green *et al.*, *J.*, 1907, 2076), whilst attempts to oxidise with air and alcoholic potassium hydroxide (Green *et al.*, *loc. cit.*) or with iodine and alcoholic potassium hydroxide (cf. Green and Baddiley, *J.*, 1908, 1725) gave none of the stilbene. 2 : 2′-Dinitro-4 : 4′-dicyanostilbene was eventually obtained in 33% yield by the action of alcoholic potassium hydroxide on 2-nitro-4-cyanobenzyl chloride (Banse, *Ber.*, 1894, **27**, 2162; cf. Walden and Kembaum, *ibid.*, 1890, **23**, 1958). Various methods were employed for reduction of 2 : 2′-dinitro-4 : 4′-dicyanostilbene to 2 : 2′-*diamino*-4 : 4′-*dicyanostilbene*; the best yield (50%) was obtained using stannous chloride in glacial acetic and hydrochloric acids. As 2-amino-4 : 4′-diamidinostilbene did not exhibit enhanced trypanocidal activity no attempt was made to prepare the corresponding 2 : 2′-diamino-diamidine, but the diamine was tetrazotised in hydrobromic acid solution and converted into 2 : 2′-*dibromo*-4 : 4′-*dicyanostilbene* by decomposition in presence of copper bronze. This, owing to its extreme insolubility, could not readily be converted into the iminoether and, after treatment with alcoholic hydrogen chloride for four weeks, over 90% was recovered unchanged.

2-*Hydroxy*-4 : 4′-*dicyanostilbene* was obtained from the corresponding amino compound by the diazo reaction, and readily yielded the iminoether and 2-hydroxy-4 : 4′-diamidinostilbene, isolated as the *dihydrochloride*.

In view of the increase of toxicity which occurs when aqueous solutions of Stilbamidine are exposed to sunlight or irradiated with ultra-violet light (Barber, Slack, and Wien, *Nature*, 1943, **151**, 107; Henry, *ibid.*, 1943, **152**, 690; Fulton and Yorke, *Ann. Trop. Med. Parasit.*, 1942, **36**, 134; Fulton, *ibid.*, 1943, **37**, 48; Kirk and Henry, *ibid.*, 1944, **38**, 99), the behaviour of 2-hydroxy-4 : 4′-diamidinostilbene dihydrochloride was studied under these conditions. After irradiation for 24 hours there was some increase in toxicity (private communication from Dr. R. Wien) but it was not so great as that observed with Stilbamidine.

Methylation of 2-hydroxy-4 : 4′-dicyanostilbene with methyl sulphate in presence of potassium carbonate and acetone readily yielded 4 : 4′-*dicyano*-2-*methoxystilbene*, which was converted by the usual method into 2-methoxy-4 : 4′-diamidinostilbene (isolated as the *dihydrochloride*). This proved to be approximately as active as Stilbamidine when administered intravenously.

Several attempts were made to prepare 2 : 2′-dihydroxy-4 : 4′-dicyanostilbene for conversion to the corresponding diamidine, by tetrazotisation of 2 : 2′-diamino-4 : 4′-dicyanostilbene and decomposition of the tetrazonium salt, but only amorphous products were isolated which resisted all attempts at purification.

The facile replacement of $-NH_2$ by $-OH$ in 2-amino-4 : 4′-dicyanostilbene and the inability to prepare a 2 : 2′-dihydroxy- from the corresponding 2 : 2′-diamino-derivative led to an attempt to synthesise 2-amino-2′-hydroxy (or methoxy)-4 : 4′-dicyanostilbene in order to determine whether an *o*-amino group might be replaced

in the presence of an *o'*-hydroxyl (or methoxyl) group. It was hoped to prepare 2-hydroxy-4-cyanobenzaldehyde from 2-nitro-4-cyanobenzaldehyde and subsequently to condense the aldehyde with 2-nitro-4-cyanotoluene. Several unsuccessful attempts were made to oxidise 2-nitro-4-cyanotoluene directly to the aldehyde with chromic acid and with selenium dioxide. Banse (*Ber.*, **1894**, **27**, 2168) obtained 2-nitro-4-cyanobenzyl alcohol by the action of fuming nitric acid on 4-cyanobenzyl alcohol, but attempts to repeat this nitration with fuming nitric acid or with potassium nitrate and sulphuric acid were unsuccessful. 2-Nitro-4-cyanobenzyl alcohol was finally obtained from 2-nitro-4-cyanobenzyl chloride (*ibid.*, p. 2162) by conversion into the acetate with potassium acetate and subsequent hydrolysis with alcoholic hydrochloric acid. Although 4-cyanobenzyl alcohol is readily oxidised to the aldehyde by nitrogen tetroxide (Ashley *et al.*, *J.*, 1942, 115), and Cohen and Harrison (*J.*, 1897, 1057) described similar oxidations of 2- and 4-nitrobenzyl alcohols, yet under the same conditions 2-nitro-4-cyanobenzyl alcohol gave only traces of the aldehyde. The aldehyde was eventually obtained in poor yield by hydrolysis of the anil formed by condensation of 2-nitro-4-cyanotoluene with 4-nitrosodimethylaniline. Attempts to reduce this nitroaldehyde to the corresponding amine by ferrous hydroxide or sodium sulphide were unsuccessful.

In view of these difficulties, it was decided to attempt the synthesis of 4 : 4'-dinitro-2 : 2'-dihydroxystilbene and then to replace the nitro by cyano groups. The oxidation of various substituted 4-nitrotoluenes to stilbenes is described by Green and Baddiley (*J.*, 1908, 1721) but we found that neither 4-nitro-2-hydroxy- nor 4-nitro-2-acetoxy-toluene was oxidised to the corresponding stilbene by alkaline sodium hypochlorite. As 4 : 4'-dinitro-2 : 2'-dimethoxystilbene had been prepared by Green and Baddiley (*ibid.*, p. 1724) by the two stage oxidation of 4-nitro-2-methoxytoluene with atmospheric oxygen and alcoholic potassium hydroxide it was thought that this intermediate might be utilised and demethylation attempted later. Oxidation of 4-nitro-2-methoxytoluene under the above conditions proceeds through the initial formation of 4 : 4'-dinitro-2 : 2'-dimethoxydibenzyl, which is oxidised to the corresponding stilbene at a higher temperature. Although the first stage was readily carried out, all attempts to accomplish the second were unsuccessful, but the required product was obtained by bromination of the dibenzyl derivative in glacial acetic acid to yield *αβ-dibromo-4 : 4'-dinitro-2 : 2'-dimethoxydibenzyl* which was converted to *4 : 4'-dinitro-2 : 2'-dimethoxydibenzyl* by heating with cuprous chloride and pyridine (cf. Bance, Barber, and Woolman, *J.*, 1943, 3). The dinitro compound was readily reduced to *4 : 4'-diamino-2 : 2'-dimethoxystilbene*, but all attempts to replace the amino by cyano groups or by bromine gave infusible solids which could not be crystallised or sublimed.

Attention was next turned to the readily accessible 5-bromo-2-methoxybenzaldehyde (Perkin *Annalen*, 1868, **145**, 304) which was condensed with 2-nitro-4-cyanotoluene to give *5-bromo-2'-nitro-4'-cyano-2-methoxystilbene*. It was hoped with this compound to settle the point whether after reduction the amino could be replaced by the hydroxyl group in presence of the *o*-methoxyl group. It was realised that the synthesis, if successful, would lead to a substituted 3 : 4'-diamidinostilbene, but it was known (*J.*, 1942, 106) that the 3 : 4'-diamidines did exhibit trypanocidal activity although of a somewhat lower degree than the symmetrical 4 : 4'-derivatives.

Reduction of 5-bromo-2'-nitro-4'-cyano-2-methoxystilbene with stannous chloride yielded, in addition to *5-bromo-2'-amino-4'-cyano-2-methoxystilbene*, another product which was soluble in alkali and had the composition of the amino compound plus an extra atom of oxygen. The constitution of this product, which readily yielded a crystalline methyl ether, was not conclusively established; but it was considered to be *5-bromo-2'-amino-5'* (or 6')*-hydroxy-4'-cyano-2-methoxystilbene* formed by alkaline hydrolysis of the corresponding nuclear chloro-compound formed as a by-product in the reduction. Attempts to replace the amino group in 5-bromo-2'-amino-4'-cyano-2-methoxystilbene by hydroxyl gave amorphous material which was insoluble in alkali and could not be crystallised or sublimed.

The availability of 5-bromo-2-methoxybenzaldehyde suggested that an attempt might be made to synthesise 6 : 6'-dihydroxy-3 : 3'-diamidinostilbene, and the method, if successful, might be modified so as to prepare the corresponding 2 : 2'-dihydroxy-4 : 4'-diamidinostilbene. Although 3 : 3'-diamidines are definitely less active than the 4 : 4'-isomerides (*J.*, 1942, 106) it was hoped that the presence of the two hydroxyl groups would enhance the activity, similarly to the effect of the single hydroxyl group on the activity of 4 : 4'-diamidinostilbene. Actually, 6 : 6'-dihydroxy-3 : 3'-diamidinostilbene unexpectedly proved to have only slight trypanocidal activity without any curative effect.

The first attempt to prepare a stilbene from 5-bromo-2-methoxybenzaldehyde was by use of the corresponding thioaldehyde (cf. Wood, *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 1234). None of the attempts to convert this into a stilbene by sublimation, heating with copper bronze, or boiling with cuprous chloride in pyridine was successful. Thermal decomposition of *3 : 3'-dibromo-6 : 6'-dimethoxybenzylideneazine* (cf. Curtius and Jay, *J. pr. Chem.*, 1889, **39**, 45; Linnell and Sharma, *Quart. J. Pharm.*, 1939, **12**, 263) yielded only traces of 3 : 3'-dibromo-6 : 6'-dimethoxystilbene which was finally obtained and converted into 6 : 6'-dihydroxy-3 : 3'-diamidinostilbene by the following method.

5-Bromo-2-methoxyphenylacetic acid was first described by Knorr and Horlein (*Ber.*, 1909, **42**, 3500) who prepared it from 5-bromo-2-methoxybenzyl alcohol by way of the chloride and cyanide. We obtained it readily from 5-bromo-2-methoxybenzaldehyde which by condensation with hippuric acid yielded *2-phenyl-4-(5'-bromo-2'-methoxybenzylidene)-5-oxazolone*. This on hydrolysis with 10% sodium hydroxide gave *5-bromo-2-methoxyphenylpyruvic acid* which was oxidised to 5-bromo-2-methoxyphenylacetic acid by alkaline hydrogen peroxide. Condensation of 5-bromo-2-methoxybenzaldehyde with sodium 5-bromo-2-methoxy-

phenylacetate in presence of zinc chloride and acetic anhydride (cf. Ruggli and Dinger, *Helv. Chim. Acta*, *loc. cit.*) yielded cis-3 : 3′-*dibromo*-6 : 6′-*dimethoxystilbene*-α-*carboxylic acid* together with a small amount of trans-3 : 3′-*dibromo*-6 : 6′-*dimethoxystilbene* formed by spontaneous decarboxylation of the *trans*-acid. The *cis*-acid, when heated in quinoline solution with copper chromite, was smoothly decarboxylated to cis-3 : 3′-*dibromo*-6 : 6′-*dimethoxystilbene*. This was readily converted into the *trans*-isomeride when heated in nitrobenzene solution with a trace of iodine (cf. Ruggli, *Helv. Chim. Acta*, 1937, **20**, 39). *cis*-3 : 3′-Dibromo-6 : 6′-dimethoxystilbene when heated with cuprous cyanide and pyridine was converted into cis-3 : 3′-*dicyano*-6 : 6′-*dimethoxystilbene* which was readily isomerised to the *trans*-compound. Demethylation of both *cis*- and *trans*-3 : 3′-dicyano-6 : 6′-dimethoxystilbene to trans-6 : 6′-*dihydroxy*-3 : 3′-*dicyanostilbene* was effected by heating to 200° with pyridine hydrochloride (Prey, *Ber.*, 1941, **74**, 1219); attempts to demethylate by heating with ethylmagnesium iodide (Späth, *Monatsh.*, 1914, **35**, 319) were unsuccessful. The dicyano compound was only slowly converted into the iminoether by treatment with alcoholic hydrogen chloride, and after four weeks nearly 30% was recovered unchanged. The diamidine *dihydrochloride* was prepared and isolated in the usual way.

Experimental.

2 : 4-*Dinitro*-4′-*acetamidostilbene*.—A mixture of 2 : 4-dinitrotoluene (9·1 g.), 4-acetamidobenzaldehyde (8·1 g.), and piperidine (6 drops) was heated at 140° for 1 hour. The melt, which soon solidified, was cooled and ground with a small amount of alcohol. The practically pure residue (7·4 g.) crystallised from glacial acetic acid in orange-red rods or needles, m. p. 262° (Ruggli and Dinger (*loc. cit.*) give m. p. 237°) (Found: N, 12·8. Calc. for $C_{16}H_{13}O_5N_3$: N, 12·8%).

2-*Nitro*-4-*amino*-4′-*acetamidostilbene*.—Hydrogen sulphide was bubbled for 2 hours through a gently refluxing mixture of 2 : 4-dinitro-4′-acetamidostilbene (10 g.) in aqueous ammonia (40 c.c.; *d* 0·880) and alcohol (120 c.c.). After cooling, the glistening red crystalline precipitate of the *amine* was filtered off and washed with alcohol and carbon disulphide. Yield, 8 g. It crystallised from glacial acetic acid in red needles, m. p. 238—239° (Found: N, 13·8. $C_{16}H_{15}O_3N_3$ requires N, 14·1%).

2-*Nitro*-4 : 4′-*diaminostilbene*.—The above acetamido compound (2 g.) was boiled under reflux for 2 hours with alcohol (20 c.c.) and hydrochloric acid (20 c.c.; *d* 1·16). Basification of the diluted mixture with aqueous ammonia (*d* 0·880) converted the orange hydrochloride into the purplish-brown diamine. This was purified by dissolving in very dilute hydrochloric acid and filtering from insoluble material. The *base* crystallised from alcohol in maroon-coloured plates or thin prisms, m. p. 156° (Found: N, 16·3. $C_{14}H_{13}O_2N_3$ requires N, 16·5%).

2-*Nitro*-4 : 4′-*dicyanostilbene*.—(*a*) A suspension of 2-nitro-4 : 4′-diaminostilbene hydrochloride, prepared from the base (5 g.) and hydrochloric acid (10 c.c.; *d* 1·16) mixed with ice, was tetrazotised by addition of sodium nitrite (3 g.) in water (10 c.c.). The mixture was poured into a solution of cuprous cyanide (5 g.) in water (15 c.c.) containing potassium cyanide (6·5 g.). Decomposition was completed by heating on the steam-bath for ½ hour and the dark chocolate-brown solid was collected, washed, and dried. Sublimation in a vacuum at 220—240° gave a small amount of golden-yellow *product* which crystallised first from glacial acetic acid and then from nitrobenzene in clusters of yellow prismatic needles, m. p. 288° (Found: N, 15·2. $C_{16}H_9O_2N_3$ requires N, 15·3%).

(*b*) A mixture of 2-nitro-4-cyanotoluene (44 g.), 4-cyanobenzaldehyde (40 g.), and piperidine (5 c.c.) was heated under reflux on the steam-bath for 36 hours. The cold melt was triturated with a little glacial acetic acid; the yellow residue crystallised from glacial acetic acid or nitrobenzene in yellow needles, m. p. 290°. Yield, 45 g. (54%) (Found: N, 15·2%).

2-*Amino*-4 : 4′-*dicyanostilbene*.—A hot solution of crystalline stannous chloride (200 g.) in hydrochloric acid (200 c.c.; *d* 1·16) was added to a suspension of 2-nitro-4 : 4′-dicyanostilbene (39·6 g.) in boiling glacial acetic acid (800 c.c.). Reduction occurred rapidly and, after further boiling for 4 minutes, the mixture was cooled and the crystalline stannichloride collected and decomposed with 25% sodium hydroxide solution. The *amine* crystallised from glacial acetic acid in yellow needles, m. p. 232°. Yield, 23 g. (65%) (Found: N, 17·1. $C_{16}H_{11}N_3$ requires N, 17·1%). Solutions of the amine in organic solvents exhibit an intense green fluorescence.

2-*Acetamido*-4 : 4′-*dicyanostilbene* was obtained in 52% yield from the amine (1·8 g.) by heating with acetic anhydride (50 c.c.) and fused sodium acetate (2 g.) at 100° for ½ hour. It crystallised from dioxan in colourless needles, m. p. 285° (Found: N, 14·4. $C_{18}H_{13}ON_3$ requires N, 14·6%).

2-*Amino*-4 : 4′-*diamidinostilbene* prepared by the usual method crystallised from methyl alcohol in yellow needles, m. p. 250°. Yield, 30% (Found: N, 24·2; equivalent by titration, 136. $C_{16}H_{17}N_5$ requires N, 25·1%; equivalent, 139·5).

2-Acetamido-4 : 4′-diamidinostilbene was obtained similarly from 2-acetamido-4 : 4′-dicyanostilbene. The *dihydrochloride* crystallised from dilute hydrochloric acid in pale yellow needles, m. p. 321° (decomp.) (Found: Cl, 16·2. $C_{18}H_{19}ON_5,2HCl$ requires Cl, 16·5%).

2-*Chloro*-4 : 4′-*dicyanostilbene*.—A suspension of 2-amino-4 : 4′-dicyanostilbene (2 g.) in hydrochloric acid (20 c.c.; *d* 1·16) was diazotised during ½ hour with sodium nitrite (1·6 g.) in water (5 c.c.). The suspension of the diazonium salt was poured into a boiling mixture of copper bronze (2 g.), hydrochloric acid (75 c.c.; *d* 1·16), and water (100 c.c.). The residue after filtering was crystallised from pyridine. Recrystallisation from nitrobenzene afforded the *compound* (0·6 g.) as puce-coloured needles, m. p. 242° (Found: N, 10·6; Cl, 13·4. $C_{16}H_9N_3Cl$ requires N, 10·7; Cl, 13·0%).

2-Chloro-4 : 4′-diamidinostilbene was prepared by the usual method; the *dihydrochloride* crystallised from methyl alcohol or hydrochloric acid in colourless needles, m. p. >320° (Found: N, 14·4; Cl, 27·1. $C_{16}H_{15}N_4Cl,2HCl,H_2O$ requires N, 14·4; Cl, 27·1%).

2-*Bromo*-4 : 4′-*dicyanostilbene*.—2-Amino-4 : 4′-dicyanostilbene (4 g.) was diazotised in 50% hydrobromic acid (40 c.c.) at 5—10° with sodium nitrite (3·2 g.) in water (5 c.c.); urea (2 g.) was then added to decompose the excess of nitrous acid. The solution, diluted with water (50 c.c.), was poured into a boiling suspension of copper bronze (2 g.) in hydrobromic acid (12%; 150 c.c.). After being collected, the *product* crystallised from pyridine in puce-coloured needles, m. p. 241°. Yield, 2·1 g. (Found: N, 8·9; Br, 25·8. $C_{16}H_9N_3Br$ requires N, 9·1; Br, 25·9%).

2-Bromo-4 : 4′-diamidinostilbene was prepared by the usual method; the crude *dihydrochloride* obtained by precipitation with hydrochloric acid (*d* 1·16) was washed with acetone, and crystallised from methyl alcohol in colourless needles (Found: N, 12·8; total halogen as Cl, 23·3. $C_{16}H_{15}N_4Br,2HCl,2H_2O$ requires N, 12·4; total halogen as Cl, 23·6%).

2-*Iodo*-4 : 4′-*dicyanostilbene*.—Ice (75 g.) was added to a solution of 2-amino-4 : 4′-dicyanostilbene (5 g.) in sulphuric acid (25 c.c.; *d* 1·84). The suspension of the amine sulphate was diazotised at 5—10° during 1 hour with sodium nitrite (4 g.) in water (15 c.c.). Urea (4 g.) was then added, and after 10 minutes the mixture was treated with potassium iodide (10 g.) in water (10 c.c.) and stirred for 3·5 hours, diluted to 250 c.c., and boiled under reflux for 30 minutes, then cooled, and the residue was collected and washed with aqueous sodium thiosulphate. The *compound* crystallised

(charcoal) from glacial acetic acid in clusters of pale yellow needles, m. p. 237°. Yield, 4·4 g. (59%) (Found: N, 7·9; I, 35·8. $C_{16}H_9N_3I$ requires N, 7·9; I, 35·6%).

2-Iodo-4 : 4′-diamidinostilbene was prepared in the usual manner; the *dihydrochloride* crystallised from an aqueous solution by addition of acetone in colourless needles (yield, 60%), m. p. >320° (Found: N, 11·5; I, 26·6. $C_{16}H_{15}N_4I,2HCl,H_2O$ requires N, 11·6; I, 26·4%).

2 : 2′-*Dinitro*-4 : 4′-*dicyanostilbene*.—(*a*) A hot solution of 2-nitro-4-cyanotoluene (5 g.) in pyridine (15 c.c.) and alcohol (150 c.c.) was treated with sodium hypochlorite solution (25 c.c. containing 16% of available chlorine) followed immediately by sodium hydroxide (50 c.c.; 33%). The mixture was heated on the steam-bath for 5 minutes, filtered, and the residue washed with water and alcohol. It crystallised from cresylic acid in pale yellow needles, m. p. 338°. Yield, 0·5 g. (11%).

(*b*) 2-Nitro-4-cyanobenzyl chloride (30 g.) in alcohol (100 c.c.) was heated on the steam-bath while alcoholic potassium hydroxide (60 c.c.; 20%) was added gradually with agitation. The residue, after filtration, was washed with water and alcohol; the *compound* crystallised from cresylic acid in yellow needles, m. p. 342°. Yield, 9·2 g. (38%) (Found: N, 17·2. $C_{16}H_8O_4N_4$ requires N, 17·5%).

2 : 2′-*Diamino*-4 : 4′-*dicyanostilbene*.—2 : 2′-Dinitro-4 : 4′-dicyanostilbene (6·8 g.), suspended in boiling glacial acetic acid (150 c.c.), was treated with a hot solution of crystalline stannous chloride (60 g.) in hydrochloric acid (60 c.c.; *d* 1·16). The mixture was boiled for 5 minutes, cooled, and filtered. The residual stannichloride was decomposed by aqueous sodium hydroxide (25%) and the *base* crystallised from dioxan (charcoal). It formed yellow needles, m. p. 291—292°. Yield, 2·8 g. (50%) (Found: N, 21·3. $C_{16}H_{12}N_4$ requires N, 21·5%).

2 : 2′-*Dibromo*-4 : 4′-*dicyanostilbene*.—2 : 2′-Diamino-4 : 4′-dicyanostilbene (1 g.) in hydrobromic acid (10 c.c.; 48%) and water (6 c.c.) was tetrazotised at 0—5° with sodium nitrite (1 g.) in water (5 c.c.). Copper bronze (0·5 g.) was added, and the mixture heated on the steam-bath until decomposition was complete. The precipitate was crystallised from pyridine; recrystallisation from nitrobenzene gave the *compound* as clusters of feathery needles, m. p. 314°. Yield, 0·8 g. (Found: N, 7·7; Br, 38·8. $C_{16}H_8N_2Br_2$ requires N, 7·3; Br, 41·0%).

2-*Hydroxy*-4 : 4′-*dicyanostilbene*.—2-Amino-4 : 4′-dicyanostilbene (6·5 g.) in boiling glacial acetic acid (250 c.c.) was treated with sulphuric acid (2N; 130 c.c.). The solution was quickly cooled and diazotised at 5—10° with sodium nitrite (2·1 g.) in water (10 c.c.) added during 1½ hours. The resulting solution was boiled for 15 minutes with sulphuric acid (55%; 450 c.c.). The mixture was diluted and cooled; the solid *product* crystallised from alcohol in lemon-yellow prismatic needles, m. p. 296°. Yield, 3·6 g. (55%) (Found: N, 11·0. $C_{16}H_{10}ON_2$ requires N, 11·3%).

2-Hydroxy-4 : 4′-diamidinostilbene was prepared by the usual method. The *dihydrochloride* crystallised from dilute hydrochloric acid in pale yellow needles, m. p. 357° (decomp.). Yield, 70% (Found: N, 15·7. $C_{16}H_{16}ON_4,2HCl$ requires N, 15·5%).

4 : 4′-*Dicyano*-2-*methoxystilbene*.—A suspension of 2-hydroxy-4 : 4′-dicyanostilbene (1·2 g.) and anhydrous potassium carbonate (1·2 g.) in methyl sulphate (2 c.c.) and acetone (20 c.c.) was boiled for 4 hours. The solid *product*, obtained by dilution with water, crystallised from dioxan in colourless feathery needles, m. p. 239°. Yield, 1 g. (78%) (Found: N, 10·7. $C_{17}H_{12}ON_2$ requires N, 10·4%).

2-Methoxy-4 : 4′-diamidinostilbene was prepared by the usual method. The *dihydrochloride* crystallised from dilute hydrochloric acid in feathery needles, m. p. 320° (decomp.). Yield, 50% (Found: N, 12·9; Cl, 16·7. $C_{17}H_{16}ON_4,2HCl,3H_2O$ requires N, 13·3; Cl, 16·9%).

2-*Nitro*-4-*cyanobenzaldehyde*.—2-Nitro-4-cyanotoluene (50 g.), 4-nitrosodimethylaniline (53 g.), and sodium carbonate (15 g.) in alcohol (250 c.c.) were refluxed for 4 days, two further additions of 4-nitrosodimethylaniline (25 g.) being made at intervals of 24 hours. The hot mixture was filtered and the black residue washed with hot water and alcohol; it yielded 17·3 g. of black crystalline anil, m. p. 206—208°. Hydrolysis with boiling hydrochloric acid (1 : 1; 170 c.c.) for 15 minutes, followed by extraction with ether and crystallisation from water, gave 6·2 g. of colourless needles, m. p. 114—115° (Found: N, 16·0. Calc. for $C_9H_6O_3N_2$: N, 15·9%).

αβ-*Dibromo*-4 : 4′-*dinitro*-2 : 2′-*dimethoxydibenzyl*.—4 : 4′-Dinitro-2 : 2′-dimethoxydibenzyl (20 g.) was boiled with glacial acetic acid (400 c.c.) and bromine (10 c.c.) for 2½ hours. The *product* (10 g.) separated from the boiling liquid in pale yellow hexagonal plates, m. p. 251° (decomp.) (Found on material recrystallised from glacial acetic acid: Br, 32·5. $C_{16}H_{14}O_6N_2Br_2$ requires Br, 32·6%). A further amount of slightly impure product, m. p. 247°, separated from the mother liquors on cooling.

4 : 4′-*Dinitro*-2 : 2′-*dimethoxystilbene*.—αβ-Dibromo-4 : 4′-dinitro-2 : 2′-dimethoxystilbene (26 g.), cuprous chloride (26 g.), and pyridine (35 c.c.) were heated at 200—220° for 2 hours. The reaction mixture was extracted repeatedly with hot hydrochloric acid (*d* 1·16) and the residue then washed with water. The *compound* crystallised from nitrobenzene in yellow prismatic needles, m. p. 275—276°. Yield, 14·2 g. (80%) (Found: N, 8·5. $C_{16}H_{14}O_6N_2$ requires N, 8·5%).

4 : 4′-*Diamino*-2 : 2′-*dimethoxystilbene*.—A hot solution of crystalline stannous chloride (16 g.) in hydrochloric acid (*d* 1·16; 16 c.c.) was added to a boiling mixture of 4 : 4′-dinitro-2 : 2′-dimethoxystilbene (2 g.) and glacial acetic acid (60 c.c.). The stannichloride quickly separated and was decomposed with 25% sodium hydroxide. The *diamine* crystallised from nitrobenzene in lemon-yellow needles (0·8 g.; 50%), m. p. 256° (Found: N, 10·3. $C_{16}H_{18}O_2N_2$ requires N, 10·4%).

5-*Bromo*-2′-*nitro*-4′-*cyano*-2-*methoxystilbene*.—A mixture of 5-bromo-2-methoxybenzaldehyde (5 g.; prepared in approximately 70% yield by bromination of 2-methoxybenzaldehyde in glacial acetic acid at 10°) and 2-nitro-4-cyanotoluene (4 g.) was heated with piperidine (0·75 c.c.) at 160° for 1½ hours. The cooled melt was extracted with cold glacial acetic acid, and the residue crystallised from glacial acetic acid. The *compound* formed yellow feathery needles (5 g.; 60%), m. p. 241° (Found: N, 8·0. $C_{16}H_{11}O_3N_2Br$ requires N, 8·0%).

5-*Bromo*-2′-*amino*-4′-*cyano*-2-*methoxystilbene*.—The above nitro compound (25 g.) in boiling glacial acetic acid (500 c.c.) was treated with a hot solution of stannous chloride (50 g.) in hydrochloric acid (*d* 1·16; 50 c.c.). The reaction mixture was diluted and filtered. The residual *product*, after extraction with dilute sodium hydroxide, crystallised from alcohol in needles, m. p. 148°. Yield, 6·8 g. (Found: N, 8·5. $C_{16}H_{13}ON_2Br$ requires N, 8·5%). An alcoholic solution of the amine exhibited an intense greenish-blue fluorescence.

Neutralisation of the alkaline filtrate gave a colourless precipitate of 5-*bromo*-2′-*amino*-5′(or 6′)-*hydroxy*-4′-*cyano*-2-*methoxystilbene* which crystallised from alcohol (charcoal) in clusters of prismatic needles (insoluble in aqueous sodium carbonate), m. p. 202° (Found: C, 55·1; H, 3·45; N, 7·8; Br, 23·1; OMe, 8·9. $C_{16}H_{13}O_3N_2Br$ requires C, 55·6; H, 3·8; N, 8·1; Br, 23·2; OMe, 8·9%). Treatment with methyl sulphate and sodium hydroxide yielded a colourless product which crystallised from dioxan in rhombs, m. p. 178°.

The above reduction was repeated using (*a*) the nitro compound (10 g.) and stannous chloride (30 g.); (*b*) the nitro compound (5 g.) and stannous chloride (6·5 g.). There were obtained 6·1 g. and 2·35 g. of crude amine and 2·05 g. and 2·15 g. of alkali-soluble material respectively.

3 : 3′-*Dibromo*-6 : 6′-*dimethoxybenzylideneazine*.—5-Bromo-2-methoxybenzaldehyde (10 g.) in boiling alcohol (130 c.c.) was treated with a solution of hydrazine prepared from hydrazine sulphate (5 g.) in 2N-sodium hydroxide (35 c.c.).

The yellow precipitate of the *azine* crystallised from pyridine (charcoal) in yellow prisms, m. p. 234°. Yield, 5 g. (47%) (Found: N, 6·8. $C_{16}H_{14}O_2N_2Br_2$ requires N, 6·8%). When the azine was heated under reduced pressure at 250—270° it sublimed unchanged. When heated at 250—270° in a vacuum with twice its weight of copper bronze a very small amount of impure 3 : 3′-dibromo-6 : 6′-dimethoxystilbene was obtained.

2-Phenyl-4-(5′-bromo-2′-methoxybenzylidene)-5-oxazolone.—5-Bromo-2-methoxybenzaldehyde (23 g.), hippuric acid (17·5 g.), fused sodium acetate (21 g.), and acetic anhydride (350 c.c.) were heated at 100° for 1½ hours. The mixture was treated with water; the *product* crystallised from glacial acetic acid in yellow needles, m. p. 179°. Yield, 26·8 g. (70%) (Found: N, 4·0. $C_{17}H_{12}O_3NBr$ requires N, 3·8%).

5-Bromo-2-methoxyphenylpyruvic acid.—The above azlactone (21 g.) was boiled under reflux with sodium hydroxide (10%; 105 c.c.) for 16 hours; the solution was diluted with water (100 c.c.) and treated at 0—10° with sulphur dioxide until acid (Congo red); benzoic acid was filtered off and the filtrate heated with hydrochloric acid (*d* 1·16; 20 c.c.). The crude acid (11·4 g.; 75%) was used directly in the subsequent oxidation. The *acid* crystallised from glacial acetic acid in colourless needles, m. p. 163° (Found: Br, 29·2. $C_{10}H_9O_4Br$ requires Br, 29·3%).

5-Bromo-2-methoxyphenylacetic Acid.—A solution of the crude acid obtained above (6·4 g.) in sodium hydroxide (10%; 150 c.c.) was stirred at 0—5° while hydrogen peroxide (20 vol.; 25 c.c.) was gradually added. After 16 hours, the solution was filtered and then acidified. The acid crystallised from methyl alcohol in colourless prismatic needles, m. p. 136°. Yield, 4·3 g. (78%) (Found: Br, 32·3. Calc. for $C_9H_9O_3Br$: Br, 32·3%).

cis-3 : 3′-*Dibromo*-6 : 6′-*dimethoxystilbene-α-carboxylic Acid.*—A mixture of 5-bromo-2-methoxybenzaldehyde (44 g.), sodium 5-bromo-2-methoxyphenylacetate (52·8 g.), zinc chloride (4·5 g.), and acetic anhydride (385 c.c.) was heated at 140—150° for 24 hours and then poured into water. After some time, the sticky product was boiled with 2N-sodium carbonate. The yellow residue of trans-3 : 3′-*dibromo*-6 : 6′-*dimethoxystilbene* crystallised from glacial acetic acid in pale yellow needles, m. p. 214° (Found: Br, 40·0; OMe, 15·9. $C_{16}H_{14}O_2Br_2$ requires Br, 40·2; OMe, 15·6%). The cold filtrate from the extraction with sodium carbonate deposited the sodium salt of the *cis*-acid. Acidification yielded this *acid* as an oil which solidified after boiling with a little benzene, and crystallised from glacial acetic acid (charcoal) in prisms, m. p. 193°. Yield, 42 g. (45%) (Found: Br, 35·8; OMe, 13·8. $C_{17}H_{14}O_4Br_2$ requires Br, 36·2; OMe, 14·0%). The crude acid (without previous treatment with benzene) crystallised directly from acetic acid in a dimorphic form (long rectangular prisms), m. p. 224°.

cis-3 : 3′-*Dibromo*-6 : 6′-*dimethoxystilbene.*—The α-carboxylic acid (9·7 g.) was added gradually to a mixture of copper chromite (1 g.) and quinoline (40 c.c.) at 210—220°. The cold reaction mixture was treated with excess of 10% hydrochloric acid; extraction with ether yielded the *product* which crystallised from methyl alcohol (charcoal) in prisms, m. p. 104°. Yield, 5 g. (58%) (Found: Br, 40·5. $C_{16}H_{14}O_2Br_2$ requires Br, 40·2%). When heated with a trace of iodine in nitrobenzene it was converted into the *trans*-isomeride, m. p. 214°.

cis- *and* trans-3 : 3′-*Dicyano*-6 : 6′-*dimethoxystilbene.*—*cis*-3 : 3′-Dibromo-6 : 6′-dimethoxystilbene (4 g.) was heated with cuprous cyanide (4 g.) and pyridine (4 c.c.) at 210° for 1·5 hours. The mixture was extracted several times with hot hydrochloric acid (*d* 1·16); the residual cis-*acid* crystallised from alcohol in colourless prisms, m. p. 153°. Yield, 1·75 g. (60%) (Found: N, 9·8; OMe, 21·4. $C_{18}H_{14}O_2N_2$ requires N, 9·7; OMe, 21·4%). When heated with nitrobenzene containing a trace of iodine it was converted into the *trans*-isomeride, which formed colourless prisms, m. p. 241°.

trans-6 : 6′-*Dihydroxy*-3 : 3′-*dicyanostilbene.*—*cis*-3 : 3′-Dicyano-6 : 6′-dimethoxystilbene (14·4 g.) was heated with dry pyridine hydrochloride (36 g.) with exclusion of moisture at 200° for 5 hours. After extraction with water, the residue was dissolved in warm dilute sodium hydroxide (charcoal). The trans-*dicyano*-compound obtained after acidification crystallised from dioxan in clusters of colourless prismatic needles, m. p. 304°. Yield, 8 g. (Found: N, 10·7. $C_{16}H_{10}O_2N_2$ requires N, 10·7%). When *trans*-3 : 3′-dicyano-6 : 6′-dimethoxystilbene was demethylated under identical conditions, it yielded the same *trans*-6 : 6′-dihydroxy-3 : 3′-dicyanostilbene, m. p. 304°.

6 : 6′-*Dihydroxy*-3 : 3′-*diamidinostilbene.*—The dicyano-compound was converted into the di-iminoether and diamidine by the method already described. The *dihydrochloride* crystallised from dilute hydrochloric acid (1 : 1) in clusters of colourless needles, m. p. above 320° (Found: N, 3·4; Cl, 16·5. $C_{16}H_{16}O_2N_4,2HCl,2H_2O$ requires N, 3·4; Cl, 17·0%).

The authors are indebted to Dr. A. J. Ewins, F.R.S., for his interest and advice, to Mr. S. Bance, B.Sc., A.R.I.C., for the semimicroanalyses, and to the Directors of Messrs. May and Baker Ltd. for permission to publish these results.

The Research Laboratories, May and Baker Ltd., Dagenham. [*Received, January 17th,* 1946.]

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113. *An Alternative Route to Stilboestrol.*

A. E. Wilder Smith.

An alternative route to stilboestrol using *n*-butyric acid and *p*-bromoanisole as starting materials is described.

The original synthesis of stilboestrol described by Dodds, Golberg, Lawson, and Robinson (*Proc. Roy. Soc.*, 1939, B, **127**, 140) was carried out from anisaldehyde as starting material, *via* α-ethyldeoxyanisoin and 3 : 4-dianisylhexane-3-ol, followed by dehydration and demethylation.

Many attempts have been made to improve on this synthesis of which account is given by Jones (*Ann. Reports*, 1943, **40**, 137). More recently Wilds and Biggerstaff (*J. Amer. Chem. Soc.*, 1945, **67**, 789) have reported a synthesis of stilboestrol from α-(*p*-methoxyphenyl)-*n*-butyric acid and anisole. Here, as in the original synthesis, α-ethyldeoxyanisoin is the key intermediate. The α-(*p*-methoxyphenyl)-*n*-butyric acid was prepared by nitration, reduction, and deamination of α-phenyl-*n*-butyric acid, so that the preparation involves a rather long series of intermediates. A further recent synthesis is reported by Rubin, Kozlowski, and Salmon (*J. Amer. Chem. Soc.*, 1945, **67**, 192) who used anisaldehyde cyanohydrin as starting material. Additional references to the subject are given in their paper.

A number of the reported routes to stilboestrol use, as the key intermediate, α-ethyldeoxyanisoin, so that a short and easy route to this substance would provide at the same time a convenient route to stilboestrol. The method of synthesis described in this communication is an extension of that used by Tiffeneau and his

collaborators (*e.g.*, *Bull. Soc. chim.*, 1931, **49**, 1758), McKenzie and his collaborators (*e.g.*, *J.*, 1926, 779; 1925, 283; 1924, 2105), and Mills and Smith (unpublished work) for the preparation of deoxybenzoins.

It has been found that ethyl α-amino-*n*-butyrate hydrochloride reacts with *p*-anisylmagnesium bromide to give β-amino-αα-dianisyl-*n*-butanol in good yield. This amino-alcohol on deamination gives the required α-ethyldeoxyanisoin, also in good yield.

$$HCl,NH_2\cdot CHEt\cdot CO_2Et \xrightarrow{MeO\cdot C_6H_4\cdot MgBr} NH_2\cdot CHEt\cdot C(OH)(C_6H_4\cdot OMe)_2 \xrightarrow{HNO_2}$$

$$CHEt(C_6H_4\cdot OMe)\cdot CO\cdot C_6H_4\cdot OMe \xrightarrow{3\ Stages} CEt(C_6H_4\cdot OH):CEt\cdot C_6H_4\cdot OH$$

Owing to the lower reactivity of the *p*-anisyl compared with the phenyl Grignard reagent (McKenzie *et al.*, *loc. cit.*) the reaction with the amino-ester hydrochloride does not proceed to completion so rapidly in boiling ether; replacement of ether by benzene as solvent, followed by refluxing for 24 hours, gives slightly better yields. The further stages of the synthesis of stilboestrol from ethyl deoxyanisoin proceeded as reported by Dodds *et al.* (*loc. cit.*) and by Wilds and Biggerstaff (*loc. cit.*).

It will readily be seen that, by variations of the substituents in the Grignard reagent used in the reaction on the amino-ester hydrochloride, the corresponding ring-substituted stilboestrols may be obtained. Similarly, by using the appropriate amino-acid, the substituents on the stilbene ethylenic carbon atoms likewise may be varied.

Experimental.

(M. ps. and b. ps. are uncorrected. The analyses are by Drs. Weiler and Strauss, Oxford.)

*α-Amino-*n*-butyric Acid.*—This was prepared by bromination of *n*-butyric acid (78% yield) followed by amination with strong aqueous ammonia (65% yield) according to the method of Abderhalden and Chang (*Z. physiol. Chem.*, 1912, **77**, 475). Esterification was carried out by suspension in absolute ethanol and passage of dry hydrogen chloride until solution was effected. Repetition of the process after removal of the alcohol gave the solid, somewhat hygroscopic ester hydrochloride.

Action of p-*Anisylmagnesium Bromide on Ethyl α-Amino-*n*-butyrate Hydrochloride.*—To the Grignard reagent prepared from magnesium (1·5 g.) and *p*-bromoanisole (11·22 g., 6 mols.) in dry ether (150 ml.) was added ethyl α-amino-*n*-butyrate hydrochloride (1·68 g., 1 mol.). The ether was then removed by distillation and replaced by an equal volume of dry benzene and the solution refluxed for 24 hours. After decomposition with crushed ice and dilute hydrochloric acid, the ether layer was separated and washed with water; the combined aqueous layers were then extracted once with fresh ether and the ether layers discarded. The aqueous layer was made alkaline with ammonia after adding excess of solid ammonium chloride, and extracted four times with ether; the combined ether layers were dried (Na_2SO_4) and then treated with dry hydrogen chloride until the solution was faint pink. After being kept at 0° overnight the pale yellow crystals of β-amino-αα-dianisyl-*n*-butanol hydrochloride were filtered off. Yield, 2·15 g. (64%). Slightly reduced yields were obtained when ether was used instead of benzene. After purification by solution in water, making alkaline with 2N-sodium hydroxide, extraction with ether, and reprecipitation from the dry ether solution by dry hydrogen chloride, the hydrochloride was recrystallised three times from absolute ethanol–light petroleum (b. p. 60—80°) and thus obtained as fine pale yellow needles, m. p. 198—199° (decomp.) (Found: C, 63·9; H, 7·2; N, 4·14; equiv. wt., 334. Calc. for $C_{18}H_{24}O_3NCl$: C, 64·1; H, 7·1; N, 4·16%; equiv. wt., 337·9).

*Conversion of β-Amino-αα-dianisyl-*n*-butanol Hydrochloride into the Free Base.*—The hydrochloride (11·7 g.) was dissolved in warm water (300 ml.) and extracted once with ether; the ether layer was separated and discarded. After making the aqueous layer just alkaline with ammonia, alcohol was added in just sufficient quantity to dissolve the precipitated oil when hot and the solution was then set aside to crystallise. To induce crystallisation it was usually necessary to seed with crystals obtained originally by keeping a solution for several weeks at 0°. Yield, 9·6 g. (92%). Several crystallisations from ethanol yielded shining flat white needles, m. p. 85—86° (Found: C, 72·0; H, 7·9; N, 4·65. Calc. for $C_{18}H_{23}O_3N$: C, 71·7; H, 7·7; N, 4·65%).

*Deamination of β-Amino-αα-dianisyl-*n*-butanol.*—The amino-alcohol (4·7 g.) was dissolved in 25% acetic acid (50 ml.) and cooled to 0°. Sodium nitrite (1·2 g.) in water (10 ml.) at 0° was added with agitation. After a few minutes an oil was precipitated. After being kept for 4 hours at room temperature the solution was neutralised with a slight excess of solid sodium bicarbonate, extracted three times with ether, and the combined ether layers were dried (Na_2SO_4). Removal of the ether gave 4·36 g. (98% of theory) of a golden oil which, on distillation, yielded a main fraction, b. p. 177—182°/0·2 mm., 4·02 g. (90% of theory). This α-ethyldeoxyanisoin was obtained crystalline according to the method of Wilds and Biggerstaff (*loc. cit.*), and after three crystallisations from light petroleum (b. p. 60—80°) and benzene melted at 46—48° to a cloudy liquid, clearing at 50—53° (Found: C, 75·9; H, 7·3. Calc. for $C_{18}H_{20}O_3$: C, 76·0; H, 7·1%).

I am indebted to the Council of the Middlesex Hospital Medical School for the provision of laboratory facilities for this work, which was carried out during the tenure of the Countess of Lisburne Memorial Fellowship.

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[*Received, January 12th*, 1946.]

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114. *The Dependence of the Viscosities of Liquids on Reduced Temperature, and a Relation between Viscosity, Density, and Chemical Constitution.*

By Leo H. Thomas.

An exponential equation is proposed representing the variation of the viscosities of liquids with reduced temperature in terms of two constants, one being characteristic of each liquid, and the other being approximately constant for all normal, non-associated liquids. The relation between the characteristic constant and molecular constitution is discussed.

In a review of the various formulæ connecting the viscosity of liquids with temperature, Srinivasan and Prasad (*Phil. Mag.*, 1942, **33**, 258) have shown that the most satisfactory are those derived by Andrade (*Nature*, 1930, **125**, 309, 582; *Phil. Mag.*, 1934, **17**, 497, 698), *viz.*,

$$\eta = Ae^{B/vT} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and its extension

$$v^{1/3}\eta = Ce^{D/vT} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where v is the specific volume, and A, B, C, and D are constants for each particular liquid. It was also shown that (1) and (2) reproduce the experimental viscosity results with equal accuracy.

Prasad (*J. Indian Chem. Soc.*, 1933, **10**, 143) indicated that the functions B/T_b and B/T_c, where T_b and T_c are the absolute boiling points and critical temperatures respectively, are approximately constant for members of the paraffin and alkyl halide series, but that the constant A decreases irregularly from member to member.

An equation incorporating reduced temperature is now proposed, *viz.*,

$$\log \eta\sqrt{v} = c + k(T_c/T - 1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where k and c are constants, and T and T_c the absolute temperatures. Rearrangement gives

$$\log \eta\sqrt{v} = (c - k) + kT_c/T = \alpha + \beta/T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

which is a modification of (1). When $T = T_c$, $c = \log \eta_c\sqrt{v_c}$, so (3) becomes

$$\log \eta\sqrt{v}/\eta_c\sqrt{v_c} = k(T_c/T - 1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

In testing the validity of (3), the critical temperatures were taken from the International Critical Tables, except those marked * which were calculated from the relationship $T_c/T_b = a - b \log [P]$ (Hertzog, *Ind. Eng. Chem.*, 1944, **36**, 997), where a and b are constants for a particular series or for a set of compounds closely related structurally, and $[P]$ is the parachor.

All specific volumes have been calculated from the reliable density–temperature equations of the International Critical Tables, or, when such equations were lacking, from the compilations of Thorpe and Rodger (*Phil. Trans.*, 1894, **185**, 397; 1897, **189**, 71) and Batschinski (*Z. physikal. Chem.*, 1913, **84**, 643) or from "Physicochemical Tables" (Castell-Evans; Griffin and Co. Ltd., 1902).

In Tables I and II, logarithms are to the base 10, and η is in 10^3 poise; α and β are the constants in equation (4).

Table I shows the agreement between the experimental and calculated values of viscosity for a few typical cases, and Table II shows the characteristic constants for 123 substances together with the maximum positive and maximum negative percentage deviations between experimental and calculated values of viscosity. The

TABLE I.

T.	η, calc.	η, found.	Error, %.
	Hexane.		
	$\alpha = -0{\cdot}6222$; $\beta = 356{\cdot}6$.		
273·8°	3·940	3·931	−0·2
282·1	3·585	3·581	−0·1
287·7	3·375	3·378	+0·1
293·0	3·196	3·202	+0·2
298·4	3·027	3·035	+0·3
303·2	2·887	2·894	+0·2
309·8	2·712	2·722	+0·4
316·5	2·554	2·557	+0·1
320·4	2·465	2·470	+0·2
325·9	2·351	2·351	±0·0
331·8	2·239	2·231	−0·4
336·6	2·152	2·143	−0·4
		Mean error	0·2
	Diethyl ketone.		
	$\alpha = -0{\cdot}6403$; $\beta = 397{\cdot}0$.		
273·5°	5·920	5·914	−0·1
282·1	5·315	5·302	−0·2
291·7	4·746	4·748	+0·0
300·1	4·331	4·328	−0·1
309·2	3·936	3·939	+0·1
317·7	3·616	3·623	+0·2
326·4	3·332	3·339	+0·2
335·4	3·073	3·079	+0·2
345·2	2·827	2·834	+0·2
354·5	2·619	2·623	+0·2
364·0	2·432	2·426	−0·2
371·8	2·294	2·279	−0·7
		Mean error	0·2

T.	η, calc.	η, found.	Error, %.
	Ethyl acetate.		
	$\alpha = -0{\cdot}7337$; $\beta = 412{\cdot}9$.		
273·2°	5·757	5·763	+0·1
281·9	5·144	5·144	±0·0
287·5	4·803	4·795	−0·2
294·4	4·427	4·418	−0·1
301·1	4·098	4·096	−0·0
309·5	3·741	3·738	−0·1
317·1	3·453	3·455	+0·1
324·1	3·220	3·224	+0·1
333·2	2·955	2·960	+0·2
341·4	2·741	2·741	±0·0
347·6	2·593	2·594	+0·0
		Mean error	0·1
	n-*Undecane.*		
	$\alpha = -0{\cdot}8549$; $\beta = 584{\cdot}3$.		
273·0°	16·78	17·24	+2·7
283·0	14·03	14·06	+0·2
293·0	11·87	11·72	−1·3
303·0	10·15	9·960	−1·9
313·0	8·760	8·643	−1·3
333·0	6·695	6·619	−1·2
353·0	5·270	5·273	+0·1
373·0	4·250	4·348	+2·3
		Mean error	1·4

TABLE II.

Substance.	T_c.	k.	Anti-log c.	Max. error. (Andrade.) +	Max. error. (Andrade.) −	+	−	Mean error, %	Approx. temp. range (° C.).	Ref.
Propane	369°	0·6189	1·158	1·3	1·6	—	—	0·8	−73—+16°	1
Butane	426	0·6124	1·214	1·1	1·9	—	—	0·9	−73—+48	,,
*iso*Butane	407	0·7164	1·258	0·8	0·9	—	—	0·4	−73—+ 4	,,
Pentane	470	0·6787	1·141	0·2	0·2	0·4	0·2	0·1	1— 33	2
*iso*Pentane	461	0·6878	1·156	0·1	0·1	0·1	0·1	0·1	1— 26	,,
Hexane	508	0·7020	1·201	0·4	0·4	0·3	0·4	0·2	1— 64	,,
*iso*Hexane	498*	0·7119	1·172	0·3	0·4	0·3	0·2	0·2	1— 55	,,
Heptane	540	0·7364	1·190	0·7	0·7	0·5	0·8	0·4	6— 92	,,
*iso*Heptane	530*	0·7298	1·180	0·4	1·0	0·5	0·9	0·4	0— 88	,,
Octane	569	0·7776	1·195	0·5	1·1	0·5	0·8	0·3	0— 122	,,
Nonane	600*	0·8198	1·166	1·1	1·0	—	—	0·8	0— 100	3
Decane	625*	0·8724	1·127	2·1	2·0	—	—	1·3	0— 100	,,
Undecane	649*	0·9003	1·100	2·7	1·9	—	—	1·4	0— 100	,,
Dodecane	667*	0·9506	1·077	3·5	2·2	—	—	1·3	0— 100	,,
Methyl formate	487	0·6832	1·245	0·3	0·1	0·2	0·3	0·1	0— 29	2
Ethyl formate	508	0·7288	1·221	0·3	0·3	0·3	0·2	0·1	0— 52	,,
Methyl acetate	507	0·7438	1·135	0·2	0·3	0·1	0·1	0·2	0— 54	,,
Propyl formate	538	0·7960	1·172	0·3	0·4	0·2	0·2	0·1	0— 77	,,
Ethyl acetate	523	0·7895	1·137	0·2	0·2	0·4	0·3	0·1	0— 75	,,
Methyl propionate	530	0·7553	1·166	0·5	0·3	0·5	0·6	0·1	0— 68	,,
Ethyl propionate	546	0·7968	1·157	0·2	0·2	0·1	0·2	0·1	0— 90	,,
Methyl butyrate	554	0·8268	1·114	0·2	0·7	0·6	0·4	0·2	0— 98	,,
Methyl *iso*butyrate	540	0·7939	1·178	0·6	0·2	0·2	0·2	0·1	0— 89	,,
Propyl acetate	549	0·8362	1·148	0·4	0·2	0·6	0·3	0·1	0— 97	,,
Butyl formate	562*	0·8776	1·149	0·9	0·7	—	—	0·5	0— 100	4
Butyl acetate	579	0·8592	1·137	1·3	0·9	—	—	0·6	0— 100	,,
*iso*Butyl acetate	561	0·8997	1·158	0·6	0·7	—	—	0·3	20— 100	5
Ethyl valerate	602*	0·8364	1·174	1·4	1·0	—	—	0·7	0— 100	4
Butyl propionate	599*	0·8453	1·179	1·5	0·9	—	—	0·6	0— 100	,,
Butyl butyrate	619*	0·8794	1·153	1·8	1·3	—	—	0·9	0— 100	,,
Butyl valerate	636*	0·9099	1·147	2·2	1·5	—	—	1·1	0— 100	,,
Ethyl heptoate	641*	0·9122	1·120	2·3	1·6	—	—	1·2	20— 100	,,
Heptyl acetate	645*	0·9685	1·137	3·7	2·9	—	—	2·0	0— 100	,,
Amyl butyrate	637*	0·9175	1·105	2·3	1·4	—	—	1·1	0— 100	,,
Ethyl bromide	504	0·6337	1·144	0·3	0·1	0·1	0·1	0·1	0— 36	,,
Propyl bromide	542*	0·6790	1·177	0·4	0·3	0·3	0·2	0·2	0— 68	,,
*iso*Propyl bromide	525*	0·7155	1·142	0·1	0·2	0·2	0·1	0·1	0— 57	,,
Butyl bromide	576*	0·6900	1·246	0·7	0·9	—	—	0·4	0— 100	6
*iso*Butyl bromide	560*	0·7578	1·179	0·5	1·2	0·4	1·0	0·4	0— 88	2
Amyl bromide	609*	0·7174	1·236	0·5	0·3	—	—	0·2	0— 100	6
Hexyl bromide	632*	0·7619	1·227	1·0	0·8	—	—	0·5	0— 100	,,
Heptyl bromide	662*	0·8054	1·180	2·2	1·3	—	—	0·8	0— 100	,,
Octyl bromide	683*	0·8565	1·135	3·5	2·2	—	—	1·2	0— 100	,,
Propanethiol	537*	0·6673	1·227	0·1	0·0	—	—	0·0	0— 30	3
Butane-1-thiol	571*	0·7028	1·185	0·7	1·0	—	—	0·5	0— 80	,,
Pentane-1-thiol	605*	0·6633	1·069	0·6	0·3	—	—	0·2	0— 100	,,
Pentane-2-thiol	585*	0·7034	1·192	0·7	0·7	—	—	0·3	0— 100	,,
Hexane-1-thiol	631*	0·7563	1·210	1·4	0·9	—	—	0·6	0— 100	,,
Hexane-2-thiol	613*	0·7471	1·175	1·4	0·7	—	—	0·5	0— 100	,,
Heptane-1-thiol	659*	0·7988	1·162	1·7	1·1	—	—	1·0	0— 100	,,
Heptane-2-thiol	640*	0·7848	1·162	1·7	1·2	—	—	0·9	0— 100	,,
Octane-1-thiol	683*	0·8494	1·104	2·2	1·7	—	—	1·2	0— 100	,,
Octane-2-thiol	664*	0·8399	1·100	2·3	1·6	—	—	1·2	0— 100	,,
Methyl iodide	519*	0·6247	1·068	0·1	0·0	0·1	0·0	0·0	0— 40	2
Ethyl iodide	550*	0·6351	1·160	0·2	0·2	0·2	0·3	0·2	0— 69	,,
Propyl iodide	584*	0·6803	1·177	0·4	0·7	0·4	0·3	0·2	0— 99	,,
*iso*Propyl iodide	564*	0·7099	1·163	0·2	0·6	0·7	0·3	0·1	0— 89	,,
*iso*Butyl iodide	599*	0·7415	1·162	1·8	0·9	1·9	0·9	0·4	0— 116	,,
Ethyl ether	467	0·6740	1·105	0·2	0·4	0·5	0·0	0·1	7— 32	,,
Methyl propyl ether	473*	0·6885	1·117	0·2	0·2	0·2	0·1	0·1	0— 35	2
Ethyl propyl ether	500	0·7354	1·118	0·2	0·5	0·2	0·3	0·1	0— 60	,,
Methyl *iso*butyl ether	488*	0·7375	1·157	0·3	0·4	0·3	0·3	0·1	0— 55	,,
Propyl ether	529*	0·7843	1·137	0·4	0·7	0·5	0·9	0·2	1— 88	,,
Ethyl *iso*butyl ether	513*	0·7857	1·133	0·3	0·4	0·2	0·1	0·1	0— 77	,,
Butyl ether	592*	0·8247	1·144	1·1	0·6	—	—	0·4	0— 100	5
Acetaldehyde	461	0·6323	1·095	0·1	0·1	0·1	0·1	0·1	0— 19	7
Propaldehyde	489*	0·8106	1·087	0·5	0·4	—	—	0·2	15— 44	,,
Butaldehyde	517*	0·7705	1·289	0·1	0·0	—	—	0·0	18— 72	,,
*iso*Valeraldehyde	532*	0·8486	1·259	0·6	0·1	—	—	0·2	21— 85	,,
Methyl cyanide	548	0·6676	1·131	0·2	0·3	—	—	0·2	16— 77	,,
Ethyl cyanide	564	0·6770	1·148	0·2	0·2	—	—	0·1	20— 93	,,
Propyl cyanide	582	0·7582	1·190	0·5	0·7	—	—	0·2	18— 113	,,
Butyl cyanide	602*	0·7814	1·264	1·0	0·2	—	—	0·2	19— 134	,,
Amyl cyanide	622	0·8050	1·291	1·5	0·1	—	—	0·3	58— 157	,,
Phenyl cyanide	699	0·7196	1·332	0·9	0·6	—	—	0·5	75— 181	,,

[References at foot of p. 577.

Substance.	T_c.	k.	Anti-log c.	Max. error. +	Max. error. −	(Andrade.) +	(Andrade.) −	Mean error, %	Approx. temp. range (° C.).	Ref.
Acetone	508	0·6718	1·164	0·2	0·3	0·5	0·2	0·1	8— 54	2
Methyl ethyl ketone	522*	0·7554	1·205	0·2	0·2	0·1	0·1	0·1	0— 76	,,
Methyl propyl ketone	547*	0·7474	1·256	0·3	0·5	0·3	0·5	0·2	0— 99	,,
Ethyl ketone	545*	0·7286	1·226	0·3	0·7	0·8	0·7	0·2	0— 99	,,
Benzene	561	0·9086	1·020	1·4	0·6	0·8	0·7	0·4	8— 75	,,
Toluene	594	0·7333	1·114	0·7	0·5	0·7	0·3	0·2	0— 107	,,
Ethylbenzene	614*	0·7157	1·179	0·6	0·4	0·8	0·3	0·2	0— 131	,,
o-Xylene	625*	0·7678	1·164	2·4	0·9	1·7	1·1	0·6	0— 141	,,
m-Xylene	620*	0·6839	1·145	0·8	0·4	0·8	0·5	0·2	0— 135	,,
p-Xylene	617*	0·7186	1·111	0·5	0·4	0·5	0·4	0·1	8— 135	,,
Propyl chloride	503	0·6808	1·213	0·6	0·6	0·7	0·4	0·3	0— 45	,,
*iso*Propyl chloride	492*	0·7286	1·112	0·0	0·0	0·1	0·1	0·0	0— 33	,,
*iso*Butyl chloride	529*	0·7734	1·162	0·1	0·2	0·3	0·3	0·1	0— 65	,,
Ethylene bromide	628*	0·8487	1·235	2·4	0·9	2·3	1·4	0·8	9— 127	,,
Propylene bromide	636*	0·8337	1·234	3·2	1·2	2·8	1·5	0·9	0— 137	,,
*iso*Butylene bromide	635*	0·9661	1·218	2·4	3·2	4·6	2·3	1·4	0— 142	,,
Allyl chloride	511*	0·6679	1·086	0·1	0·2	0·2	0·2	0·1	1— 42	,,
Allyl bromide	544*	0·6671	1·115	0·2	0·3	0·3	0·2	0·1	0— 69	,,
Allyl iodide	585*	0·6821	1·125	0·4	0·3	0·4	0·3	0·2	0— 98	,,
Diallyl	498*	0·6984	1·070	0·3	0·3	0·2	0·4	0·1	0— 56	,,
Isoprene	475*	0·6507	1·169	0·3	0·1	0·1	0·1	0·1	0— 32	,,
*β-iso*Amylene	473*	0·6152	1·085	0·1	0·1	0·1	0·1	0·1	0— 33	,,
Methylene chloride	518*	0·6401	1·212	0·3	0·1	0·2	0·1	0·1	0— 38	,,
Chloroform	536	0·6659	1·294	0·1	0·2	0·2	0·2	0·1	0— 57	,,
Carbon tetrachloride	556	0·9155	1·155	1·0	0·7	1·1	0·6	0·3	7— 74	,,
Ethylene chloride	565*	0·8494	1·215	1·0	0·5	1·0	0·6	0·4	0— 81	,,
Ethylidene chloride	529*	0·7286	1·170	0·1	0·1	0·1	0·2	0·1	7— 55	,,
1:1:2:2-Tetrachloroethane	626	0·9942	1·069	2·1	1·2	—	—	0·8	0— 80	5
Chlorobenzene	632	0·7191	1·125	0·9	2·0	—	—	0·5	0— 120	8
o-Chlorotoluene	650*	0·7544	1·195	1·6	1·3	—	—	0·9	0— 100	5
m-Chlorotoluene	654*	0·7127	1·120	1·6	1·5	—	—	1·0	0— 100	,,
Bromobenzene	670	0·7230	1·104	2·5	1·7	—	—	1·4	0— 142	8
m-Bromotoluene	682*	0·7319	1·129	2·3	1·5	—	—	1·2	0— 100	5
p-Bromotoluene	683*	0·7122	1·180	0·8	0·3	—	—	0·4	30— 100	,,
Fluorobenzene	559	0·7814	1·109	1·8	1·7	—	—	0·6	9— 81	8
Iodobenzene	721	0·7409	1·032	3·2	3·3	—	—	1·4	5— 149	,,
Methyl sulphide	503	0·6038	1·174	0·2	0·3	0·1	0·1	0·1	0— 36	2
Ethyl sulphide	557	0·6881	1·165	0·2	0·3	0·3	0·6	0·1	0— 88	,,
Acetic anhydride	569	0·8613	1·348	2·4	0·9	2·1	1·0	0·6	0— 133	,,
Propionic anhydride	615*	0·8728	1·220	4·4	1·5	3·1	1·7	1·0	0— 165	,,
Ethylene oxide	465	0·6287	1·212	1·2	0·9	—	—	0·5	−50— + 9	9
Carbon disulphide	546	0·4671	1·291	0·8	0·3	0·5	0·2	0·2	0— 46	2
Bromine	575	0·6489	1·339	0·3	0·2	0·4	0·3	0·1	1— 56	,,
Thiophen	590	0·7521	1·104	1·3	0·3	0·9	0·5	0·4	0— 80	,,
*cyclo*Hexanone	654*	1·0359	1·245	2·0	3·1	—	—	1·2	14— 90	10
*cyclo*Hexane	554	1·1270	1·127	0·9	1·3	—	—	0·6	11— 76	11
*cyclo*Hexyl chloride	626*	0·9445	1·297	0·9	0·2	—	—	0·3	48— 133	,,
Anisole	642	0·8668	1·058	0·2	0·2	—	—	0·1	56— 142	,,
Average values (Thorpe and Rodger's results only)	—	—	—	0·6	0·5	0·6	0·4	0·2	—	—
			β.	*α*.						
Nitromethane	—	417·3	0·6334	0·2	0·6	—	—	0·2	0— 80	12
Nitroethane	—	448·6	0·6634	0·3	0·3	—	—	0·2	19— 109	,,
Nitropropane	—	480·9	0·7049	0·4	0·3	—	—	0·2	15— 122	,,
Nitrobutane	—	501·0	0·7120	0·7	0·6	—	—	0·4	15— 143	,,
Nitropentane	—	535·0	0·7591	1·6	0·9	—	—	0·6	21— 161	,,
3-Methylnitrobutane	—	568·3	0·8002	0·7	0·4	—	—	0·2	40— 155	,,
Nitrobenzene	—	533·9	0·6029	0·8	0·5	—	—	0·4	96— 208	13
Propyl nitrite	—	344·1	0·6534	0·0	0·1	—	—	0·0	16— 46	12
Butyl nitrite	—	384·9	0·6928	0·3	0·6	—	—	0·2	16— 71	,,
Amyl nitrite	—	414·2	0·6689	0·5	0·4	—	—	0·3	19— 99	,,
*iso*Amyl nitrite	—	389·5	0·6319	0·1	0·0	—	—	0·0	13— 79	,,
Nitric acid	—	518·1	0·8863	0·6	0·4	—	—	0·3	18— 69	,,
Benzyl cyanide	—	571·6	0·6585	0·6	0·5	—	—	0·2	90— 200	7
Ethyl cyanoacetate	—	645·7	0·8515	0·2	0·3	—	—	0·2	111— 201	,,
Diphenyl	—	684·8	0·8555	0·2	0·2	—	—	0·1	139— 210	13
*cyclo*Hexyl bromide	—	598·0	0·7816	0·4	0·2	—	—	0·2	89— 155	11
Phenyl ethyl ether	—	556·8	0·8081	0·2	0·5	—	—	0·2	78— 165	13
Acetophenone	—	543·8	0·6507	0·2	0·2	—	—	0·1	99— 188	,,
*cyclo*Hexane	—	475·7	0·7464	0·3	0·1	—	—	0·1	19— 80	,,
p-Methyl*cyclo*hexanone	—	592·8	0·7778	2·1	1·5	—	—	1·6	20— 80	5
Methylene bromide	—	383·5	0·4907	0·1	0·2	—	—	0·1	19— 91	14
Trichloroethylene	—	324·1	0·4274	0·1	0·0	—	—	0·0	30— 80	5
Pentachloroethane	—	670·1	1·0260	1·4	1·6	—	—	1·0	0— 80	,,
Chloral	—	525·4	0·8385	1·0	0·6	—	—	0·3	22— 95	7
Furfural	—	614·2	0·9137	3·1	2·8	—	—	1·7	0— 100	15
Propane-2-thiol	—	384·0	0·6892	0·1	0·2	—	—	0·1	0— 40	3

Calculated T_c probably unreliable

corresponding deviations when using equation (2), taken from Andrade's data, are given for purposes of comparison. Mean percentage deviations are listed in col. 9. The constants c and k were evaluated by application of Campbell's " zero sum " method (*Phil. Mag.*, 1920, **39**, 177; 1924, **47**, 816).

It appears that (3) fits the experimental results as accurately as do the Andrade equations, and it is clear that the introduction of the v term into the variable, log η, has an effect well within the limits of experimental accuracy in the determination of viscosity. This might have been anticipated, for, within any temperature range, the variation in viscosity is many times greater than the corresponding change in density. However, (3) has the marked advantage that $c = \log \eta_c\sqrt{v_c}$ is approximately a constant for all the normal non-associated substances examined. Of the 123 liquids for which critical temperatures are known or can be calculated as above, 96 possess values of $\eta_c\sqrt{v_c}$ differing from the mean figure 1·167 by less than 6% and 112 by less than 9%. The remaining 11 liquids, which include benzene, carbon disulphide, chloroform, and bromine, differ from the mean by 9—16%.

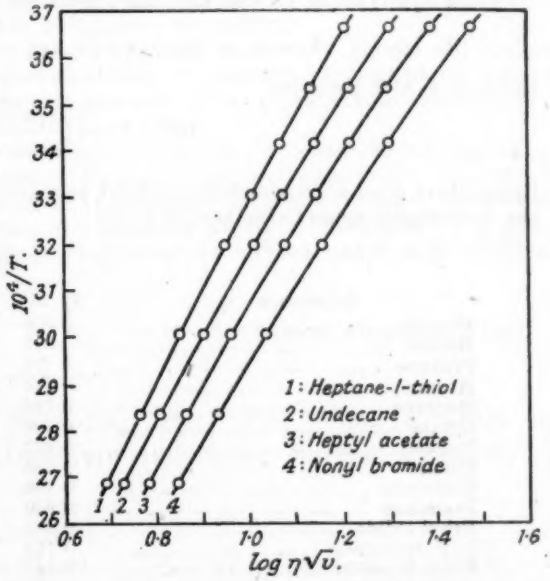
It therefore becomes possible, as a fair approximation, to express the viscosity of a liquid by an equation involving only one characteristic constant; *i.e.*,

$$\log \eta\sqrt{v} = 0{\cdot}0670 + k(T_c/T - 1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The calculated value of the intercept c for a particular compound depends on the accuracy of measurement of η, v, and T_c, and considerable extrapolation is involved in its evaluation. Possibly then, for most of the substances, (6) is within the limits of experimental accuracy; but this not at all likely for, *e.g.*, benzene, chloroform, and bromine.

It is noteworthy that the mean value of c for the 49 compounds whose critical temperatures are known is 1·168 as compared with 1·166 for the 74 compounds whose critical temperatures were calculated as above.

The agreement between the calculated values of viscosity and the experimental results of Thorpe and Rodger (*locc. cit.*) is highly satisfactory, the average mean error being 0·2%. These measurements were carried out at 0—100° on liquids of low molecular weight and therefore low boiling point. Similar measurements have since been made on liquids of higher boiling point, notably by Bingham and his co-workers. The agreement here is not so satisfactory, and the log $\eta\sqrt{v}$–$1/T$ curves are decidedly convex to the $1/T$ axis, the curvature for the range 0—100° being the more pronounced as the temperature drops and as the boiling points of the liquids increase (see figure). Such a curvature is also exhibited by a small number of the higher-boiling liquids, *e.g.*, the alkylene bromides (Thorpe and Rodger). The typical case of *n*-undecane is shown in Table I.



Examination of the mean deviations between experimental and calculated viscosities shows that this departure from linearity occurs with all liquids having mean errors greater than 0·3—0·4%. In fact, the curvature is so regular that the mean error over a given range in temperature may be taken as a rough measure of its extent.

In certain cases, *e.g.*, hexane, the log $\eta\sqrt{v}$–$1/T$ curves are concave to the $1/T$ axis, but the mean errors are only 0·1—0·3%, probably within the limits of experimental accuracy. It seems fairly certain then that the simple exponential expressions (1) and (5) are true only at temperatures approaching the boiling point.

Equation (6) enables one to calculate $\eta\sqrt{v}$ for a given compound at any temperature (say, the b. p.) from one measured value at another temperature T, provided T_c can be estimated as above. Let

$$[\log_{10} \eta_c v_c] - 0{\cdot}0670 = \Delta \log_{10} \eta_c\sqrt{v_c}$$

Then it may easily be shown that

$$\Delta \log \eta_B\sqrt{v_B} = \Delta \log \eta_c\sqrt{v_c}\left[1 - \frac{T_c/T_B - 1}{T_c/T - 1}\right]$$

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[1] Lipkin, Davison, and Kurtz, *Ind. Eng. Chem.*, 1942, **34**, 976. [2] Thorpe and Rodger, *locc. cit.* [3] Bingham and Fornwalt, *J. Rheol.*, 1930, **1**, 372. [4] Bingham and De Turck, *ibid.*, 1932, **3**, 479. [5] After the compilation of Bingham and Spooner (*Physics*, 1933, **4**, 387). [6] Bingham and Stookey, *J. Amer. Chem. Soc.*, 1939, **61**, 1625. [7] Friend and Hargreaves, *Phil. Mag.*, 1944, **35**, 619. [8] Meyer and Mylius, *Z. physikal. Chem.*, 1920, **95**, 349. [9] Maass and Boomer, *J. Amer. Chem. Soc.*, 1922, **44**, 1709. [10] Huckel and Wunsch, *J. pr. Chem.*, 1935, **142**, 225. [11] Friend and Hargreaves, *Phil. Mag.*, 1944, **35**, 57. [12] *Idem, ibid.*, 1944, **34**, 810. [13] *Idem, ibid.*, 1944, **35**, 136. [14] *Idem, ibid.*, 1943, **34**, 643. [15] Bingham and Rogers, *J. Rheol.*, 1932, **3**, 113.

Put $T_c/T = 2$, then, since $T_c/T_B \approx 1{\cdot}5$, $\Delta \log \eta_B\sqrt{v_B} = \frac{1}{3}\Delta \log \eta_c\sqrt{v_c}$, but as the average value of $\Delta \log \eta_c\sqrt{v_c}$ is 0·0158, we have $\Delta \log \eta_B\sqrt{v_B} = 0{\cdot}0079$, or $\Delta\eta_B v_B = 1{\cdot}8\%$.

Hence the viscosity of a given liquid at its b. p. may be calculated from a given value at the reduced temperature $\frac{1}{2}$ with an average accuracy of approximately 1·8%. For toluene, for example, $\frac{1}{2}T_c = 24°$ C. and $T_B = 120°$ C., and as $\Delta \log \eta_c\sqrt{v_c} = 0{\cdot}0201$,

$$\Delta \log \eta_B\sqrt{v_B} = 0{\cdot}0201/2 = 0{\cdot}0100, \text{ or } \Delta\eta_B\sqrt{v_B} = 2{\cdot}3\%.$$

The Dependence of k *on Molecular Constitution.*—In equation (3), putting $T_c/T = 2$, we have

$$\log (\eta\sqrt{v})_{T=\frac{1}{2}T_c} = c + k \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

so $(c + k)$ is a measure of the function $\log \eta\sqrt{v}$ at the reduced temperature $T_r = \frac{1}{2}$.

Examination of the constants in Table II shows that k increases fairly regularly with each increment of CH_2, and, as far as can be ascertained, is the same for all homologous series. The increment in k for CH_2, *i.e.*, k_{CH_2} was found for the paraffin series by applying Campbell's zero-sum method to the nine equations of the type $k_{butane} = k_{2H} + 4k_{CH_2}$ for the hydrocarbons from butane to dodecane. This procedure gives $k_{CH_2} = 0{\cdot}039$. By a similar method, the alkyl bromides give a value 0·031, thiols 0·037, esters 0·031, and cyanides 0·040. Other series were not taken into the calculation, for no data beyond those for the fourth members are available. The mean $k = 0{\cdot}036$ was adopted as the most probable value.

From equation (8), for two successive members of any homologous series, we may write

$$k_2 - k_1 = \log (\eta_2\sqrt{v_2})_{T=\frac{1}{2}T_c} - \log (\eta_1\sqrt{v_1})_{T=\frac{1}{2}T_c} - (c_2 - c_1) \approx 0{\cdot}036$$

But $c_2 - c_1 \approx 0$, therefore

$$10^{(k_2 - k_1)} = \left(\frac{\eta_2\sqrt{v_2}}{\eta_1\sqrt{v_1}}\right)_{T=\frac{1}{2}T_c} = 10^{0{\cdot}036} = 1{\cdot}086$$

Hence there is an approximately constant increase in $\eta\sqrt{v}$ at a reduced temperature of $\frac{1}{2}$ from one member of any homologous series to the next of 8·6%.

TABLE III.

Substance.	k, calc.	k, found.	$(\eta\sqrt{v})_{300}$, calc.	$(\eta\sqrt{v})_{300}$, found.	Error, % (to nearest 1%).
Propane	0·606	0·619	1·61	1·61	± 0
Butane	0·642	0·612	2·17	2·19	+ 1
Pentane	0·678	0·679	2·82	2·77	− 2
Hexane	0·714	0·702	3·65	3·69	+ 1
Heptane	0·750	0·736	4·65	4·62	− 1
Octane	0·786	0·778	5·92	5·96	+ 1
Nonane	0·822	0·820	7·74	7·71	− 0
Decane	0·858	0·872	9·91	9·93	+ 0
Undecane	0·894	0·900	12·8	12·4	− 3
Dodecane	0·930	0·951	16·0	15·7	− 2
Ethyl iodide	0·656	0·635	4·10	3·93	− 4
*iso*Butyl iodide	0·728	0·741	6·21	6·37	+ 3
Ethyl bromide	0·647	0·634	3·21	3·08	− 4
Amyl bromide	0·755	0·717	7·00	6·78	− 3
Octyl bromide	0·863	0·856	14·8	14·1	− 5
Propanethiol	0·649	0·667	3·80	4·13	+ 9
Hexane-1-thiol	0·757	0·756	7·98	8·26	+ 3
Octane-1-thiol	0·829	0·849	13·3	13·5	+ 1
Acetone	0·675	0·672	3·43	3·40	− 0
Diethyl ketone	0·783	0·729	5·09	5·18	+ 2
Methyl formate	0·693	0·683	3·16	3·32	+ 5
Ethyl acetate	0·765	0·790	4·32	4·39	+ 2
Propyl acetate	0·801	0·836	5·40	5·67	+ 5
Ethyl valerate	0·873	0·836	8·83	8·17	− 8
Heptyl acetate	0·945	0·968	14·3	14·8	+ 4
Amyl butyrate	0·945	0·918	13·4	11·9	−13
Methyl propyl ether	0·696	0·689	2·94	2·79	− 5
Butyl ether	0·840	0·825	7·66	7·26	− 5
Methyl cyanide	0·666	0·668	4·15	4·03	− 3
Amyl cyanide	0·810	0·805	8·65	9·44	+ 9
Isoprene	0·638	0·651	2·45	2·50	+ 2
Diallyl	0·674	0·698	3·25	3·10	− 5
*iso*Butyl chloride	0·733	0·773	4·23	4·53	+ 7
Methylene chloride	0·716	0·640	3·86	3·54	− 9
Carbon tetrachloride	0·898	0·916	6·81	7·00	+ 3
Chloroform	0·807	0·666	5·03	4·33	−16
Ethyl benzene	0·706	0·716	6·40	6·61	+ 3
m-Xylene	0·706	0·684	6·61	6·14	− 8
Chlorobenzene	0·725	0·719	7·41	7·03	− 5
m-Bromotoluene	0·747	0·732	10·4	9·66	− 8

The above argument clearly applies equally well to any other reduced temperature, the value of log $\eta\sqrt{v}$ for CH_2 being less or greater than 0·036 according as T_r is greater or less than $\frac{1}{2}$. Thus at corresponding temperatures for any homologous series, there is a constant percentage increase in $\eta\sqrt{v}$ from one member to the next, this percentage being 8·6 at the reduced temperature $\frac{1}{2}$.

In view of the constancy of k_{CH_2}, it seemed reasonable to assume that k could be evaluated from a list of atomic and structural constants. By proceeding in the usual way, the following list has been drawn up:

C = − 0·462	Cl = 0·340	Double bond = 0·478
I = 0·335	S = 0·043	C_6H_5 = 0·385
H = 0·249	Br = 0·326	CO (ketones and esters) = 0·105
O = 0·054		CN (cyanides) = 0·381

The measure of agreement between the calculated and observed values of k is shown for a few typical cases in Table III. Clearly, by employing the above list of constants, $\eta\sqrt{v}$ for a substance at any temperature may be evaluated, provided T_c can be estimated as above. Thus, *e.g.*, at 27° C., we can write $\log (\eta\sqrt{v})_{300} = 0{\cdot}067 + k(T_c/300 - 1)$.

Table III also shows the percentage deviations between the values of $\eta\sqrt{v}$ at 27° C. so calculated, and the actual values [as calculated from (3)] at that temperature. In ascertaining the mean percentage error thus involved, all the substances listed in Table II were included, with the exception of the following whose k values could not be calculated: carbon disulphide, thiophen, *cyclo*hexane, *cyclo*hexanone, and *cyclo*hexyl chloride.

Large errors are exhibited by benzene (52%), ethylene chloride (27%), ethylene bromide (45%), propylene bromide (28%), *iso*butylene bromide (60%), *iso*valeraldehyde (29%), and anisole (32%).

The exceptional behaviour of benzene and the alkylene halides was also observed by Thorpe and Rodger (*locc. cit.*). The behaviour of the latter may be due to the accumulation of "negative" groups, and it may be significant that parachor and molecular refractivity anomalies are also associated with such molecules (Mumford and Phillips, *J.*, 1929, 2112).

The remaining 108 liquids, of which 72 show errors of less than 5%, 91 less than 9%, and 102 less than 14%, show a mean error of 5%. The agreement is perhaps better than could have been expected in view of the nature of the approximations made, and the uncertainty involved in the evaluation of T_c. At least, the method is not without practical value in viscometry, where choice of viscometer capillary dimensions for a given liquid would be facilitated. Further, the temperature–viscosity behaviour can be predicted from the relationship $\beta = kT_c$.

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[*Received, February 7th*, 1946.]

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115. *The Properties of Freshly Formed Surfaces. Part VI. The Influence of Temperature and Concentration on the Dynamic and Static Surface Tensions of Aqueous Decoic Acid Solutions.*

By C. C. Addison.

The solubility in water of decoic acid at 20° has been found by a surface tension method to be 0·0050%, and the static surface tension of the saturated solution is 40·2 dynes/cm. at 20°. The vibrating jet shows no appreciable fall in tension from the pure water value at any concentration, and a modified drop-weight method has been employed to measure the time required for the accumulation of the adsorbed layer of decoic acid. Diffusion has been found to proceed over periods from about 10 seconds up to several minutes depending on concentration. These times are greatly in excess of that normally attributed to the diffusion process, but are in accord with the times forecast by the general equation given in Part V. Diffusion equilibrium is followed by a very slow fall in the static surface tension. Measurements have been carried out over the temperature range 10—40°. Both dynamic and static surface tensions show an unusually large increase with temperature, particularly in the more dilute solutions, although the duration of the diffusion process is insensitive to temperature.

Since the fall in concentration in the surface layer of an expanding drop due to expansion of the surface cannot be replenished immediately by diffusion of decoic acid from the bulk, the tension varies with the rate of expansion of the drop. Temperature changes have a negligible effect on the tension at an expanding surface, in sharp contrast to the effect at a non-expanding surface.

The vibrating jet studies reported in Parts I—IV (J., 1943, 535; 1944, 252, 477; 1945, 98) have established that for aqueous solutions of alcohols of chain length up to eight carbon atoms, the process of diffusion to the air–water surface is complete within 0·1 second for all concentrations except the most dilute, where the possible fall in tension from the pure water value is small. The minimum depth from which solute must be drawn to form the surface excess depends upon its solubility, which diminishes rapidly as chain length increases. This factor outweighs the increase in the velocity of migration of adsorbate to the surface, so that the time required for the establishment of diffusion equilibrium actually increases with chain length (Part IV, *loc. cit.*). An adsorption velocity–time equation was given in Part V (J., 1945, 354) which can be used to forecast this time where it lies outside the surface age range of the vibrating jet. Employing this equation, it appeared that if the solubility of the straight-chain alcohols of 10 carbon atoms and more was sufficient to give rise to an

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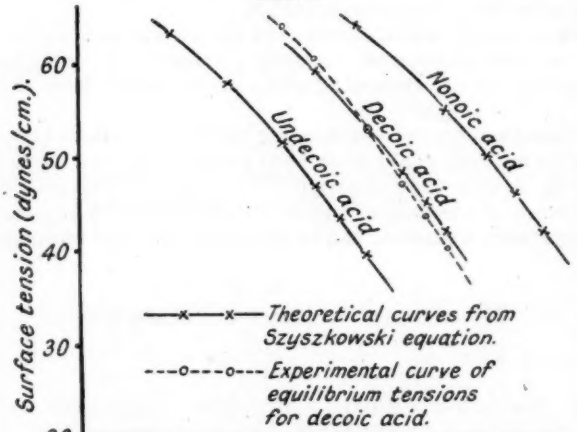
appreciable lowering of tension by a soluble film, the diffusion process would extend over minutes, and other experimental methods would then be available. Unfortunately, the solubility barrier restricts the study of the adsorption of the longer-chain alcohols. However, it is already known (Part IV, *loc. cit.*; Adam, "Physics and Chemistry of Surfaces," Oxford Univ. Press, 3rd Ed., p. 50) that, for static surfaces at least, the surface behaviour of primary alcohols and carboxylic acids is similar, and the slightly greater solubility conferred by the carboxyl group has enabled the decoic acid system to be studied experimentally. The order of time required for completion of diffusion has been recently reported (Addison, *Nature*, 1945, **156**, 600) and lies in the range calculated for *n*-decyl alcohol, so that the similarity in behaviour between the acids and alcohols extends to dynamic surfaces also.

The solubility of decoic acid has been found experimentally to be 0·0050% at 20°. At this concentration the static surface tension is 40·2 dynes/cm., yet the vibrating jet showed no appreciable fall in tension below the pure water value at surface ages up to 0·1 second. However, preliminary experiments with drops of the solution formed rapidly (in about 2 seconds) on a calibrated orifice showed that the subsequent time required for drops identical in size to fall away was accurately reproducible, and was a function of concentration and the drop weight. The method was therefore applied as described below. It has provided a means of studying changes in surface tension, clearly due to diffusion, by an entirely independent static method, and of comparing the conclusions with those reached employing the dynamic vibrating jet method. Again, the vibrating-jet technique cannot be readily adapted to investigation of the temperature effect in solutions, owing to the shortening of the jet which occurs at higher temperatures (Addison, *Phil. Mag.*, 1945, **36**, 73). With the present method it has been possible to measure dynamic and static surface tensions over the temperature range 10—40°.

FIG. 1.



EXPERIMENTAL.

The drop pipette used was similar to that described by Powney and Addison (*Trans. Faraday Soc.*, 1937, **33**, 1243) except that the air leak was replaced by a pressure screw. The liquid under test was maintained at the desired temperature by surrounding the reservoir bulb with a water jacket. It was found possible over the temperature range 10—40° to maintain the drop at the same temperature as the pipette liquid by surrounding it with an annular space filled with the liquid used for circulation through the water jacket. As the temperature coefficient of surface tension is large for decoic acid solutions, this temperature range was adequate. At temperatures above 40° the readings became erratic; this was probably due to evaporation of water from the drop surface rather than to temperature fluctuations.

Formation of Drop.—Liquid was forced from the jet by means of a pressure screw attached to the top of the pipette. Drops were brought to the desired size by observing their formation through a microscope fitted with an eyepiece scale. The tension when the drop fell away was determined from the drop weight, the correction factors of Harkins and Brown (*J. Amer. Chem. Soc.*, 1919, **41**, 499) being used. In timing the drop life, a small drop was first formed on the orifice; this was brushed off by a piece of absorbent paper, leaving a fresh surface flush with the orifice, and the drop to be tested was immediately expelled. By this means the starting of the stopwatch could be made to coincide with the formation of a drop possessing a fresh surface, with an error not exceeding 2 seconds.

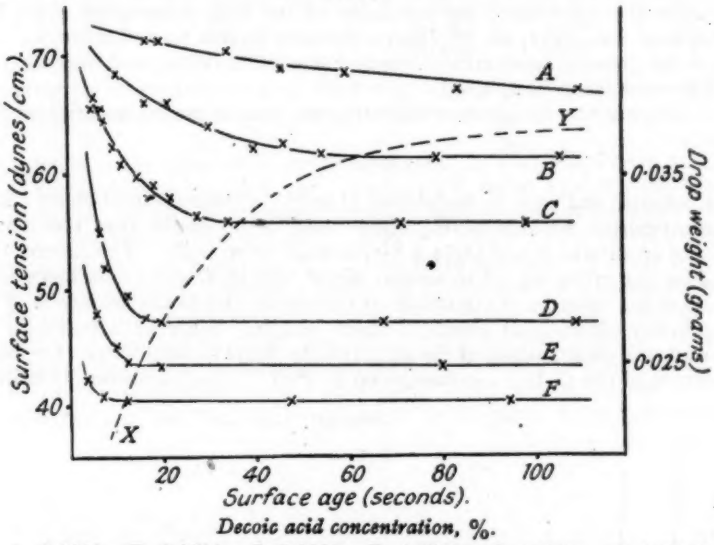
Purity of Decoic Acid.—In view of the high surface activity of any impurities of similar chain length which may be present with the decoic acid, a knowledge of the state of purity of the sample employed was of first importance. The material used was "*n*-capric acid" supplied by Messrs. B.D.H. Ltd., and had m. p. 30·2°. The acid was vacuum distilled and the distillate collected in eight separate fractions but no variation in m. p. or surface activity could be detected between the various fractions. The m. p. of the pure acid is given as 30° (Görgey, *Annalen*, 1848, **66**, 290), 31·3° (Krafft, *Ber.*, 1882, **15**, 1696) and 31·5° (Houben, *Ber.*, 1902, **35**, 3592). Although any impurities present were therefore in small proportion, the m. p. could not be accepted as a guarantee of adequate purity. As the main requirement in this work was that the surface tensions should be truly representative of the C_{10} acid, the theoretical curves relating surface tension (γ) and concentration (c) for acids of this order of chain length were calculated by using Szyszkowski's equation (*Z. physikal. Chem.*, 1908, **64**, 385), *viz.*, $\gamma/\gamma_0 = 1 - B \log (c/a + 1)$. The constant B is given by Szyszkowski as 0·411 for the straight-chain acids, and is independent of chain length. A similar value (0·407) has been reported for the straight-chain alcohols (Part IV, *loc. cit.*). The term a is constant for a given adsorbate, and is reduced by a constant factor for each additional carbon atom in the chain. The Szyszkowski values of a for the C_3—C_6 acids are tabulated below:

Carbon atoms in molecule (n).	a.	a_n/a_{n+1}.	Carbon atoms in molecule (n).	a.	a_n/a_{n+1}.
3	0·165	—	9	11·1 × 10^{-5}	3·38
4	0·051	3·24	10	3·30 × 10^{-5}	3·38
5	0·015	3·40	11	0·975 × 10^{-5}	3·38
6	0·0043	3·49			

Values of a determined for the straight-chain alcohols having 1—8 carbon atoms (Part IV, *loc. cit.*) have shown that though slight variations exist in a_n/a_{n+1}, the ratio shows no tendency to increase or decrease with chain length. The mean of the Szyszkowski values for a_n/a_{n+1} (3·38) was therefore employed to determine a for the longer chain lengths. By using the values for B and a thus obtained, the theoretical surface tension–concentration curves for the C_9—C_{11}

acids, nonoic, decoic and undecoic, were calculated, and are shown as full curves in Fig. 1. The equilibrium tension–concentration curve obtained experimentally with the sample used is superimposed as a broken line. The close agreement between the experimental and the theoretical decoic acid curve confirms the absence of other surface-active impurities, and of impurities capable of influencing the surface activity of the decoic acid.

FIG. 2.

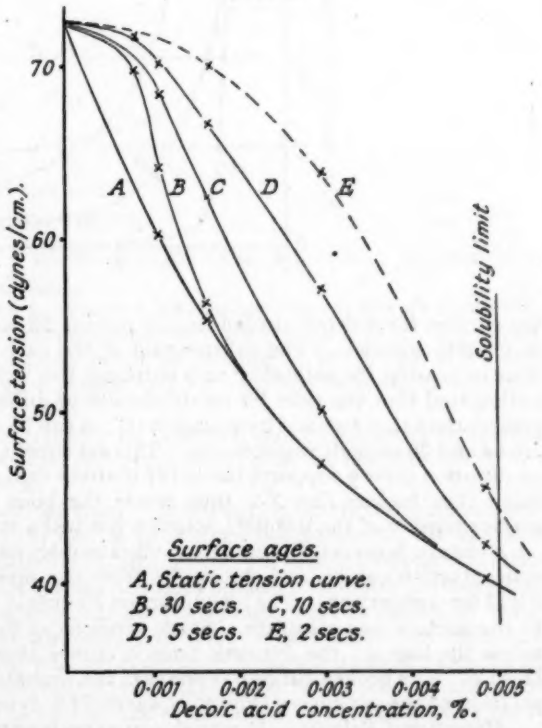


Decoic acid concentration, %.

A, 0·0008. B, 0·0011. C, 0·0017. D, 0·0030. E, 0·0042. F, 0·0049.

Solubility of Decoic Acid.—The very low solubility of decoic acid in water rendered difficult the preparation of standard solutions, since it was not possible to detect visually whether a trace of decoic acid added to a large volume of water had dissolved, or still adhered to the walls of the vessel. A modified form of the surface-tension technique used (Part IV, *loc. cit.*) for the slightly soluble alcohols was therefore employed. A saturated solution was prepared by adding excess decoic acid to 1 l. of water redistilled twice through Pyrex glass, warming it to 35° to melt the acid, swirling for one hour, and cooling again to 20°. A little of this solution was filtered, and the static surface tension corresponding to diffusion equilibrium (*i.e.*, the level portion of the γ–t curves, Fig. 2) was measured. The solution was then left in contact with decoic acid for 24 hours at 20°, and the static surface tension again measured to confirm saturation. The result obtained was 40·2 dynes/cm. at 20°. Solutions were then prepared by adding known amounts of the acid to 1 l. of water, and dissolving them at 35°. The γ–t curve was then obtained, and a solution giving a static tension higher than 40·2 dynes/cm. could be regarded as standard. A number of such solutions were so tested, and the static surface tension plotted against the concentration (curve *A*, Fig. 3). Extrapolation of this curve to 40·2 dynes/cm. gave the solubility of decoic acid in water at 20° as 0·0050%. Further standard solutions could then be made up conveniently from the saturated solution by dilution. Measurements were normally made on solutions freshly made up, but check tests on solutions kept for up to six days showed no ageing effects.

FIG. 3.



Results and Discussion.

Surface Tension–Time Curves.—The results obtained at 20° are recorded in Fig. 2. The vertical axes show the drop weights measured as well as the surface tension, so that the order of experimental error is clear from the curves. Drop weights were accurate to the fourth place of decimals, and the error in this direction is negligible. The slight displacement of the points from an ideal curve is probably due to errors in timing the drop life, since up to 2 seconds were required for drop formation. Also, during these 2 seconds the surface is expanding rapidly, and little accumulation of adsorbate can occur at the surface. However, it is clear from the experimental results that the position of the surface tension–time curve for any particular concentration can be fixed with accuracy, and that owing to the high surface activity of decoic acid, small changes in concen-

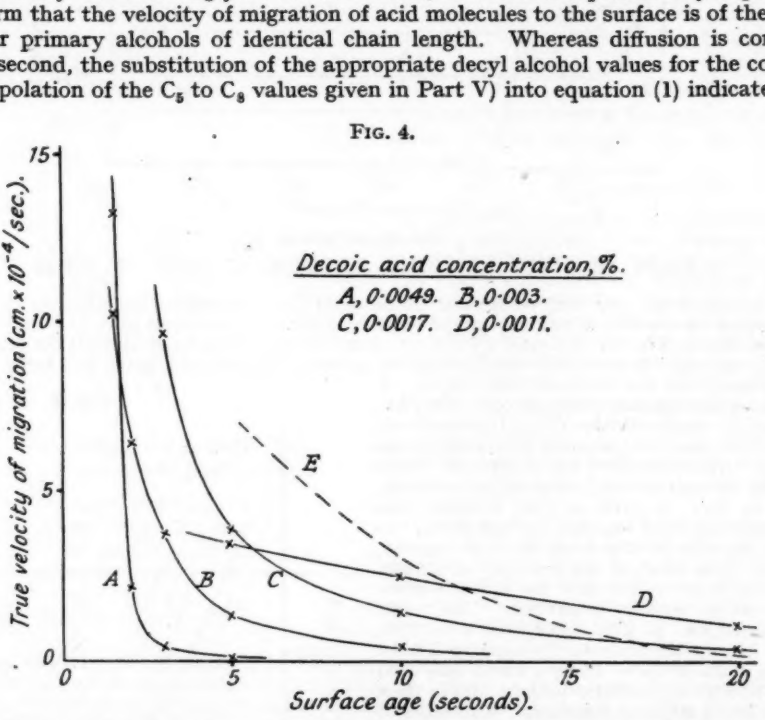
tration produce large changes in dynamic as well as static tension. Each curve consists of an initial fall from the pure water value (which is more rapid as concentration increases, but can be followed satisfactorily almost up to the solubility limit), followed by a very slow fall beyond the broken line XY. This slow fall is probably due to rearrangements in the established surface layer of the type known for other long-chain adsorbates (Alexander, *Trans. Faraday Soc.*, 1941, **37**, 15; and references therein to earlier work). This drift, which was not of direct interest in the present experiments, was not studied in detail, and over the range of time recorded in Fig. 2 this slow fall in tension can be ignored.

It is of interest to compare the duration of the diffusion process found experimentally with that forecast by the general equation

$$v = a^n t e^{-akt} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

relating adsorption velocity (v) and time (t), developed in Part V for the straight-chain alcohols. This equation was deduced from vibrating-jet measurements, where there is no doubt that the tension changes are due solely to accumulation of adsorbate at the surface by diffusion from bulk. The shorter-chain carboxylic acids have not been studied by the vibrating jet in similar detail, but sufficient preliminary experiments have been conducted to confirm that the velocity of migration of acid molecules to the surface is of the same order as the reported values for primary alcohols of identical chain length. Whereas diffusion is complete for n-octyl alcohol within 0·1 second, the substitution of the appropriate decyl alcohol values for the constants a, k and n (obtained by extrapolation of the C_5 to C_8 values given in Part V) into equation (1) indicates that diffusion to

FIG. 4.



the surface for n-decyl alcohol should require 22 seconds for completion in 0·0011% solution, and 12 seconds in 0·002% solution. The substitution of the carboxyl group renders the molecule rather more hydrophilic, thus increasing the solubility and reducing the velocity of migration to the surface. It was therefore to be anticipated that the time for establishment of diffusion equilibrium in the case of decoic acid would be rather greater than that forecast by equation (1); it can be deduced from Fig. 2 that the values for these concentrations are 64 and 30 seconds respectively. This agreement between the order of results obtained and those anticipated on diffusion theory supports the belief that the initial fall in tension (Fig. 2) is the result of diffusion to the surface. The broken line XY thus traces the boundary between dynamic and static surface tensions. The surface tension of the 0·0008% solution reached a static value of 63·5 dynes/cm. after about 6 minutes.

Dynamic tensions obtained from vibrating-jet measurements have been reported in Parts II—IV as tension-concentration curves, and the results from the present work at 20° have been collected in a similar form in Fig. 3 for comparison. The "equilibrium" curve A is a plot of the tensions obtained immediately after diffusion to the surface was complete. Static tensions at higher surface ages (not considered in detail here) would lie below the line A; the dynamic tension curves above line A resemble closely in form those reported in Parts II—IV. The broken curve E represents the probable position of the 2-second curve, as indicated by the extrapolation of the γ–t curves (Fig. 2) towards 72·8 dynes/cm. at zero surface age.

Migrational Velocity.—It was shown experimentally in Part IV for the amyl—octyl alcohols that over the available concentration range, $d\gamma/dc$ (as determined from the slope of the equilibrium curve A, Fig. 3) was approximately proportional to the time t_1 required for the establishment of diffusion equilibrium, and thus the *mean* velocity of migration of adsorbate molecules (V), determined from $V = -100M(d\gamma/dc)/KTt_1$, was constant. It was deduced theoretically in Part V that if experiments could be carried out at sufficiently high dilution,

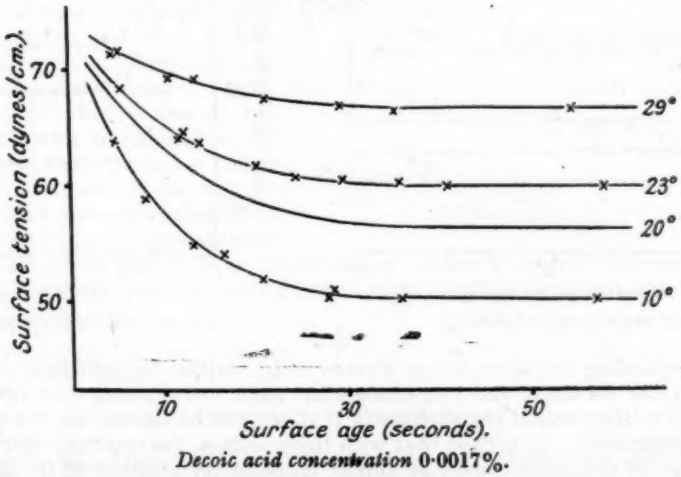
the value of V would fall with decreasing concentration, and that this effect would be more pronounced as chain length increased. The latter conditions are satisfied by the decoic acid system, and the values of V given below show the expected fall with dilution.

c, %.	$d\gamma/dc$.	t, secs.	$V \times 10^4$, cm./sec.	c, %.	$d\gamma/dc$.	t, secs.	$V \times 10^4$, cm./sec.
0·0011	9500	64	1·05	0·0030	4600	20	1·62
0·0017	7200	37	1·37	0·0049	3000	12	1·77

The decoic acid system therefore falls beyond the range of applicability of the migrational velocity term, and the values of V in this table cannot be accepted as representative of decoic acid for comparison with the alcohols.

True Velocity of Migration.—The adsorption mechanism given in Part V has been used to determine the true velocity of migration of decoic acid molecules to the surface at 20° and at four concentrations, and the velocity–time curves are given in Fig. 4. With the practical technique used it was not possible to obtain the peaks of the curves, but the die-away sections available are clearly part of a family of v–t curves resembling those recorded in Part V, and can be represented by equation (1); n and k are functions of chain length only, and a is proportional to the concentration c at high dilution. Attempts to reproduce the experimental curves by assuming n, k or a to have exactly the alcohol value were unsuccessful, indicating that the polar group has an influence on the manner of variation of n and k with chain length as well as on the ratio a/c. For example, the broken curve E (Fig. 4) is the theoretical v–t curve for n-decyl alcohol in 0·0011% solution, and is shown for comparison with curve D, deduced from experimental results on a decoic acid solution of the same concentration. The general agreement is satisfactory, but the slight increase in hydrophilic nature due to the carboxyl group is

FIG. 5.



Decoic acid concentration 0·0017%.

reflected in curve D in a lower velocity of migration at low surface ages, and the greater time required for the curve to reach zero velocity, *i.e.*, completion of diffusion.

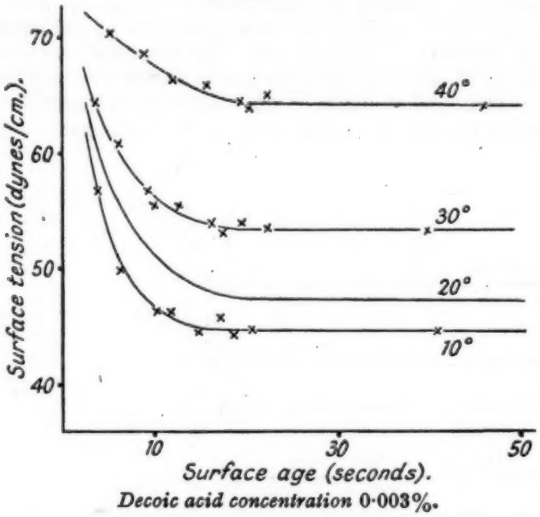
Influence of Temperature on Static and Dynamic Tensions.—Surface tension–surface age curves in the range 10—40° have been obtained experimentally for three concentrations, and are shown in Figs. 5—7. At a concentration of 0·0042% (Fig. 7) measurements were not made below 20° because of the danger of exceeding the solubility of decoic acid; some experiments at 10° gave erratic and high surface tensions, probably due to separation of decoic acid from solution.

Two general conclusions are apparent from each set of graphs: (*a*) relatively small changes in temperature have a profound effect on both static and dynamic tensions, and (*b*) change in temperature has little effect on the time required for the establishment of diffusion equilibrium.

Considering (*a*), the temperature coefficient increases with dilution. In a 0·0017% solution the mean temperature coefficient is approximately 1 dyne/cm. per degree, and is in marked contrast with the values not exceeding 0·1 dyne/cm. per degree found (Powney and Addison, *loc. cit.*) for sodium dodecyl sulphate solutions, and with the commonly accepted order of values for both solutions and pure liquids. In 0·003% concentration the coefficient is only a little less, and the tension again approaches the pure water value at the higher temperatures. Although it is generally accepted in the case of solutions that increase in temperature results in a decrease in adsorption and a consequent increase in the surface tension, it appears most improbable that relatively small temperature increases of this order can almost completely inhibit the process of adsorption; on the other hand, the increase in the kinetic agitation of the surface molecules may be sufficient to prevent orientation of the surface excess of decoic acid at both dynamic and static surfaces, and may thus prevent the surface excess being fully reflected in the surface tension. It is also significant that at a concentration of 0·0042% the temperature coefficient is less, and a temperature–tension curve derived from Fig. 7 indicates that the tension will not reach the water value at higher temperatures.

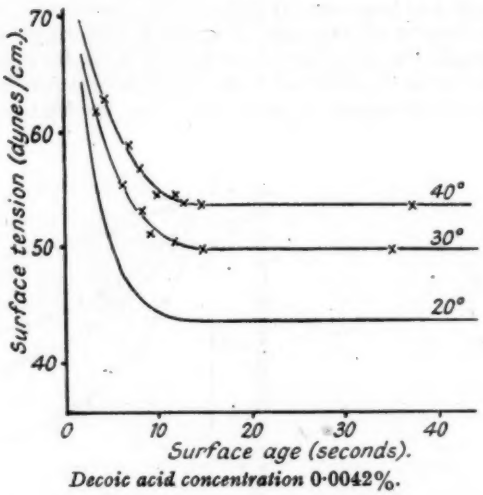
Considering (*b*), two opposing factors may operate in these systems. First, the rate of accumulation of adsorbate at the surface was shown in Part III (*loc. cit.*) to be proportional to the free surface energy as defined by $\gamma_t - \gamma_E$, where γ_t is the dynamic tension at time t, and γ_E is the static value. γ_E for decoic acid increases rapidly with rising temperature, and therefore the free surface energy, the rate of accumulation of adsorbate, and the velocity of migration to the surface (v) should all decrease as the temperature rises. Secondly, if the high static tensions at the higher temperatures can be taken to indicate a correspondingly small surface excess of decoic acid, the depth d from which adsorbate is drawn should also decrease with rising temperature. Since the time t_1 required to build up the surface layer is a function of the ratio d/v, then proportionate alteration of d and v with increasing temperature provides a satisfactory explanation of the constancy of t_1 in the case of the 0·0042% solution. However, the application of this reasoning to the lower concentrations involves the doubtful assumption that at higher temperatures little surface excess exists, and it is probable that a more complex mechanism operates. The influence of temperature changes on the surface tension of solutions has received but little attention, particularly at high dilutions, and it is proposed to investigate this aspect further.

FIG. 6.



Decoic acid concentration 0·003%.

FIG. 7.



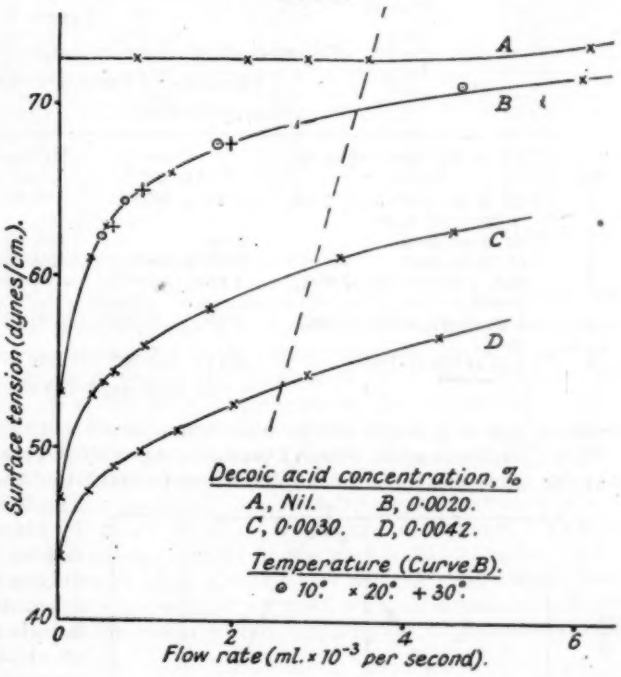
Decoic acid concentration 0·0042%.

Adsorption to an Expanding Surface.—It has already been verified for solutions of dyestuffs (Gibby and Addison, J., 1936, 119) and for soaps and long-chain alkyl sulphates (Powney and Addison, *Trans. Faraday Soc.*, 1938, **34**, 356) that in drop-weight measurements, if 12 seconds be allowed for the formation of each drop, mechanical errors are eliminated. It is clear that with these solutes, the constant decrease in surface concentration due to expansion of the surface must be almost immediately replenished by diffusion from the bulk. With the decoic acid solutions discussed above, diffusion continues for so long that the drop-weight method as frequently employed in stalagmometry (*i.e.*, slow formation of drop until the drop weight is equivalent to the surface tension) cannot be used. The apparatus was adapted for these experiments by replacing the pressure screw by an air leak formed from a piece of capillary glass tubing drawn out to a fine thread which could be broken off to give the required rate of expansion of drop. The experimental results obtained for three concentrations are tabulated below, and the flow rate calculated therefrom is plotted against the surface tension in Fig. 8. It should be emphasised that this tension value has no direct significance in terms of either static or dynamic tensions in the sense in which these terms are used earlier in this paper.

Concn., %.	Temp.	Drop weight, mg.	Secs. per drop.	Concn., %.	Temp.	Drop weight, mg.	Secs. per drop.
Pure water	20°	43·3	50, 20, 15, and 12	0·0030	20°	31·0	80
,,	,,	43·7	7	,,	,,	31·4	60
,,	,,	44·3	3	,,	,,	31·7	48
0·0020	10	36·7	75	,,	,,	32·5	32
,,	,,	37·8	50	,,	,,	34·8	20
,,	,,	40·1	22	,,	,,	36·0	11
,,	,,	42·3	9	,,	,,	37·0	8
,,	20	35·9	100	,,	,,	39·8	5
,,	,,	37·0	72	0·0042	20	27·5	80
,,	,,	38·0	44	,,	,,	28·4	44
,,	,,	39·0	30	,,	,,	28·9	31
,,	,,	40·9	15	,,	,,	29·6	21
,,	,,	42·6	7	,,	,,	30·6	15
,,	30	37·0	60	,,	,,	31·8	11
,,	,,	38·4	40	,,	,,	33·2	7·5
,,	,,	40·0	20				

The broken line in Fig. 8 represents the flow rate corresponding to 12 seconds per drop. It will be seen from the pure water curve that a small mechanical error is introduced at higher flow rates, and the apparent slight increase in tension due thereto will be present in the curves for the decoic acid solutions also. The significant range is therefore that which lies between the broken line and zero flow rate, and in no case is the surface tension independent of flow rate. The tension values recorded in Fig. 8 for zero flow rate are the static values already determined for these concentrations, and clearly form the limiting points for the expanding drop curves. The surface tensions obtained by this technique are the resultant of two factors, *i.e.*, the accumulation of a surface excess of decoic acid due to diffusion from the bulk solution, and the diminution of the surface concentration by expansion of the surface. At the higher flow rates, much of the acid diffusing to any given unit area of surface will be removed from that unit area by expansion; the surface concentration will be maintained at a low level, and the surface tension will be correspondingly high. As the flow rate (which is an index of the rate of expansion of the surface) decreases, the surface is able to maintain a higher concentration of adsorbate, and the surface tension decreases accordingly, until at zero flow rate it is equivalent to the static tension. Each curve was obtained at 20°, but points on the 0·0020% curve have also been determined at 10° and 30°. It is of interest that the latter points lie, within experimental error, exactly on the 20° curve. In view of the large temperature coefficient found for non-expanding surfaces, it appears that the power of an adsorbed decoic acid layer to lower surface tension is altered fundamentally by expansion of the surface, and the quantitative study of adsorption to expanding surfaces will form the subject of a later communication.

FIG. 8.



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[*Received, November 26th*, 1945.]

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116. *An Improved Analysis of Fuming and Concentrated Sulphuric Acid by Water Titration.*

By J. C. D. BRAND.

The direct determination of sulphur trioxide in fuming sulphuric acid by titration with water (Parker, *J. Soc. Chem. Ind.*, 1917, **36**, 692) has been improved and shown to give results of considerable precision. The titration is applied further (*a*) to the analysis of concentrated sulphuric acid with a high order of accuracy, and (*b*) to the preparation of a standard normal solution of sulphuric acid without reference to analytical standards such as sodium carbonate or potassium iodate.

THE direct estimation by water of the sulphur trioxide contained in fuming sulphuric acid was proposed and carried out by Setlik (*Chem. Ztg.*, 1889, **13**, 1670) and by Parker (*loc. cit.*). However, in spite of the fact that Parker was able to show that the accuracy thus attainable is higher than that reached by any other means, the method does not seem to have gained much currency and receives only brief mention in works which describe the methods of analysis of oleum. This method for the determination of oleum strength amounts in principle to titration with distilled water of the " free " sulphur trioxide of the acid to an end-point at which the cooled liquid no longer fumes in contact with air. The familiar way of determining the strength of an oleum is by alkalimetry: the amount of alkali consumed by the sulphur trioxide, however, is only a small fraction of that required by the great bulk of sulphuric acid, and errors in estimation of the trioxide are commensurably magnified. It is clear that the water titration, which estimates sulphur trioxide directly, possesses an advantage over the alkali method; moreover, the distilled water of the titration is already an absolute standard.

The procedure of titration differs somewhat from that described by Parker (*loc. cit.*). Improved results were obtained by using a small drop in titration and by keeping the temperature of the liquid during the search for the end-point below 10°, rather than below 45° as recommended previously. Anhydrous sulphuric acid fumes perceptibly at about 13°, and an oleum will be over-titrated if the temperature at which the end-point

is reached is not lower than this. Analyses of oleum by water and by alkali are compared in Table I. An oleum which contains another substance dissolved in it cannot, however, be analysed straightforwardly by water titration, for most solutes combine chemically with a proportion of the sulphur trioxide of the oleum, and this quantity escapes estimation by water. *Direct* application of the water method is confined to pure

TABLE I.

The strength of oleum by water-titration and by alkalimetry.

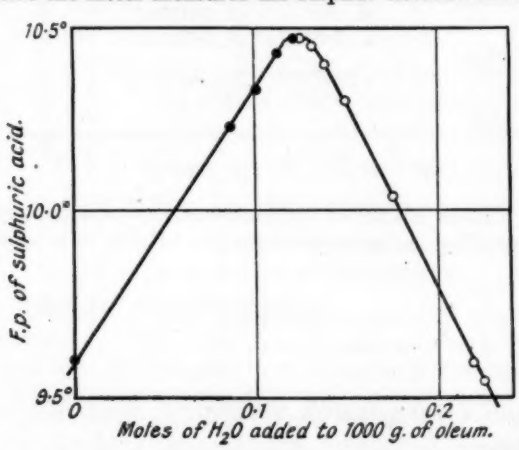
(Density of water = 0·998 g./ml. at 20°.)

	Water-titration.				% H_2SO_4 by alkalimetry.	
No.	Ml. of H_2O per 100 g. of oleum.	Mean, ml.*	H_2SO_4, %.	"Free" SO_3, %.	Observed.	Mean.
1	3·98, 3·98, 4·00, 3·97, 3·95, 3·98, 3·95, 3·97	3·97 ± 0·01	103·96	17·6	103·9, 104·0	104·0 ± 0·1
2	3·84, 3·84, 3·84	3·84	103·83	17·0	103·9, 104·0	103·9 ± 0·1
3	3·07, 3·08, 3·05	3·07 ± 0·01	103·06	13·6	103·1, 103·0, 103·0, 102·9	103·0 ± 0·1
4	1·668, 1·667, 1·667, 1·664, 1·663	1·666 ± 0·002	101·66	7·39	—	—
5	0·495, 0·498, 0·498, 0·495, 0·487	0·495 ± 0·003	100·49	2·19	—	—
6	0·200, 0·195, 0·195	0·197 ± 0·002	100·20	0·87	100·1, 100·2, 100·1	100·1 ± 0·1

* The error quoted is the mean deviation.

oleum by this fact, which will be examined in detail in a subsequent paper.

The Correctness of the Water Titration.—Agreement between the alkali and the water titration is not proof that the latter measures the sulphur trioxide content of an oleum exactly, but verification of this is possible. The freezing point of anhydrous sulphuric acid is lowered by the addition of either water or sulphur trioxide. It is desired to find, therefore, whether, under the conditions of titration prescribed below, fuming ceases abruptly when a liquid of maximum freezing point is reached. That this is so is confirmed by experiment, the results of one series of which are displayed in the figure: water was added, in amount shown along the horizontal axis, to an oleum containing 1·00% of sulphur trioxide. The freezing points of the acids which were or were not seen to fume are marked by dots or circles respectively. As the freezing point of the liquid rose, fuming diminished, and no fume was seen upon the liquid after the freezing point maximum was reached. This observation was made at the freezing point of the acid (10·5°), but a fume could be seen over the terminal acid upon raising the temperature to only 13° or 14°, and Parker's statement (*loc. cit.*) that anhydrous sulphuric acid does not fume below 30° is therefore inexact. Provided, however, that the temperature at which the end-point is sought is below 10°, water titration gives an exact measure of the "free" sulphur trioxide contained in an oleum.



Determination of the Strength of Concentrated Sulphuric Acid.—Attempts to analyse concentrated sulphuric acid by direct titration with oleum to the first appearance of a fume gave unpromising results, but the alternative

TABLE II A.

Determination of the strength of concentrated sulphuric acid.

(Density of water at 20° : 0·998 g./ml.)

	Standard oleum.							
Acid.	Ml. H_2O per 100 g.	G. of oleum used.	Titre of sample used, ml.	Conc. H_2SO_4 (g. used).	Water-titration of mixture, ml.	Water (ml.) present in conc. H_2SO_4.	H_2O, %.	H_2SO_4, %.
1	2·767	36·66	1·015	50·92	0·433	0·582	1·14	98·86
		35·99	0·996	60·51	0·320	0·676	1·12	98·88
		52·51	1·454	52·95	0·860	0·594	1·12	98·88
								98·87 ± 0·01
				(By alkali: 98·8, 98·9%.)				
2	3·01	68·43	2·060	71·23	1·087	0·973	1·36	98·64
		48·31	1·454	69·53	0·500	0·954	1·37	98·63
		32·21	0·970	49·48	0·280	0·690	1·39	98·61
		50·09	1·508	101·21	0·115	1·393	1·37	98·63
								98·63 ± 0·01

TABLE II B.

Acid.	Standard oleum. G. of oleum used.	Standard oleum. Ml. of H_2O per 100 g.	Conc. H_2SO_4 (g. used).	Wt. of mixture analysed, g.	Water-titration of mixture, ml.	Water (ml.) present in conc. H_2SO_4.	H_2O, %.	H_2SO_4, %.
3	150·0	10·00	250·0	*a.* 21·72	0·554	0·260	1·91	98·09
				b. 25·84	0·659	0·309	1·92	98·08
				c. 23·19	0·595	0·275	1·89	98·11
	250·0	10·00	400·0	*a.* 59·31	1·593	0·688	1·89	98·11
				b. 72·03	1·923	0·847	1·91	98·09
				c. 48·86	1·300	0·579	1·92	98·08
	197·0	6·963	213·0	*a.* 22·78	0·535	0·227	1·91	98·09
				b. 75·80	1·787	0·749	1·90	98·10
				c. 31·35	0·737	0·312	1·91	98·09
								98·09 ± 0·01

(The mean deviation is quoted for each series of results.)

method of back-titration was satisfactory. A weighed quantity of oleum of known strength was mixed with a weighed amount of concentrated sulphuric acid, and the remaining sulphur trioxide in the mixture estimated by water. The difference between the titration of the oleum and of the oleum–concentrated acid mixture is equal to the volume of water contained in the aqueous acid, from which its strength may be calculated (Table II). As the results quoted show, concentrated sulphuric acid may be analysed by this determination of the water content to within about 0·02% H_2SO_4, or with several times the accuracy of volumetric alkalimetry. The method can be used with advantage for the analysis of sulphuric acid stronger than about 90% H_2SO_4: application is still confined to pure acids which contain no dissolved substance.

Preparation of a Standard Aqueous Solution of Sulphuric Acid.—It is a straightforward matter to analyse a pure oleum by water so that its strength is known to ± 0·01% H_2SO_4. By dilution of this acid with water (without loss of fume) one may obtain an aqueous acid of strength known to one part in 10,000 parts. A very weak oleum, containing 1% or less of sulphur trioxide, can be diluted with water without a significant loss of fume. By diluting a weighed amount of weak oleum, three approximately N-solutions of sulphuric acid were prepared, and the strengths of each found independently by use of a standard solution of potassium iodate. The results were as follows:

100·20% H_2SO_4 was diluted with water to the following concn.	Concn. found by reference to KIO_3.
0·8908N	0·8902N
1·043N	1·042N
1·189N	1·189N

It is therefore possible to prepare a standard solution of sulphuric acid by this means without resort to standard analytical substances other than distilled water.

EXPERIMENTAL.

Oleum was prepared by distilling sulphur trioxide in an all-glass Pyrex apparatus from a strong (commercial) oleum into concentrated sulphuric acid; purification was repeated until the product was colourless. No residue remained upon ignition of the acids, which contained less than 0·003% of sulphur dioxide. The type of flask used for storage had a ground glass cone at the neck, and was closed by a ground glass cap.

Method of Titration.—Distilled water was added from a micro-burette, graduated to read to 0·02 ml., the tip of which was drawn out into a capillary so that the drop size was about 0·01 ml. Choice of the amount of oleum used in an estimation depends upon the strength of the oleum under analysis and the precision required; with the burette used it was clearly desirable that a titration should not be of less than 0·5 ml. About 25 g. of oleum were used to obtain the comparatively crude results 1—3 of Table I, whereas more than 150 g. was sometimes taken for the remaining analyses. The oleum was titrated in a glass-stoppered conical flask, to which water was added in such amounts that there was no escape of fume. Fume within the flask was absorbed by vigorous shaking after each addition, and the acid cooled in ice; the temperature at the end-point of a titration must be below 10°. Fuming diminished near the end of a titration. When necessary the liquid was tested to see whether it still fumed by blowing a puff of air (from a bellows) into the flask, through a tube held with its opening only a few mm. above the surface of the liquid. Any fume was thereby swept out of the flask leaving the air within momentarily clear, but, if the liquid was still an oleum, fume formed again rapidly and was seen as a mist upon the surface. Water was added dropwise, and this observation repeated at each step until no fume could be detected over the liquid. Near the end-point the fume which formed was slight and was seen only in a good light. Titrations are best carried out in bright daylight, the flask being held for inspection against a dark background. Immediately before the end-point a mere wisp of fume develops, which lies on the surface of the oleum in the centre of the flask, and is seen from an eye-level slightly above the plane of the surface of the liquid.

If, in testing for the end-point, the air within the flask is changed too often the effect of the moisture introduced become detectable. Air used to locate the end-point cannot be dried, since the fume forms by reaction of sulphur trioxide with water vapour. The number of times air may be blown over the liquid without effect upon the titration obviously depends upon the humidity, and the volume of air enclosed in the flask. (0·005 Ml. of water, *i.e.*, half a drop in titration, is contained in some 300 ml. of air of maximum humidity at 20°.) For comparison, the results of Table I are expressed in ml. of water consumed by 100 g. of oleum. Denoting this quantity by v, the strength of the oleum (if the density of water be taken as unity) is $(100 + v)\%H_2SO_4$, or $(v/0·225)\%$ "free" SO_3.

Analyses by alkali were made by dilution of the acid to give a roughly N-aqueous solution, which was analysed by titration with normal alkali, methyl-red being used as indicator. Estimations were not reproducible to better than one part in 1000 parts, the consequent error being 0·1% H_2SO_4 in the calculated oleum strength. To obtain more accurate

results by alkalimetry, however, the method of gravimetric titration with sodium carbonate (Richards and Hoover, *J. Amer. Chem. Soc.*, 1915, **37**, 108) needs to be adopted.

The author wishes to thank Professor G. M. Bennett, who initiated this work, and the Chief Scientific Officer of the Ministry of Supply for permission to publish the results.

KING'S COLLEGE, LONDON. [*Received, January 23rd*, 1946.]

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117. *New Syntheses of Heterocyclic Compounds. Part VI. Triazafluorenes and Azaphenazines from 4-Chloro-3 : 5-dinitropyridine.*

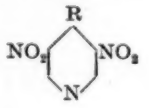
By V. A. PETROW and J. SAPER.

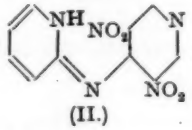
N-(3′ : 5′-*Dinitro-4′-pyridyl*)-2-*aminopyridine* (II), prepared by interaction of 4-chloro-3 : 5-dinitropyridine (I; R = Cl) and 2-aminopyridine, has been found to lose readily the elements of nitrous acid to furnish a new base, 1-*nitro*-3 : 9 : 12-*triazafluorene* (III; R = NO_2). Reduction gave the *amino*-derivative (III; R = NH_2), which furnished 13-*hydroxy*-3 : 12-*diaza*-12 : 13-*dihydrocarbazole*-1 : 9-*diazole* (IV) on diazotisation.

Condensation of phenyl-o-phenylenediamine with (I; R = Cl) gave N-(3 : 5-*dinitro*-4-*pyridyl*)-N′-*phenyl*-o-*phenylenediamine* (V; R = Ph), converted by loss of the elements of nitrous acid into 1-*nitro*-5-*phenyldihydro*-3-*azaphenazine* (VI), and passing on reduction into 1-*amino*-5-*phenyl*-3-*azaphenazonium chloride* (VII; R = NH_2).

IN Parts III and IV of this series (Petrow and Rewald, *J.*, 1945, 313, 591) it was shown that 4-chloro-3 : 5-dinitropyridine (I; R = Cl) could, like picryl chloride, be used in the synthesis of phenoxazines and phenthiazines. We now record an extension of the synthetical uses of this reagent to include the preparation of the hitherto unknown 3 : 9 : 12-triazafluorenes and 5-phenyl-3-azaphenazines.

In an attempt to prepare new bases of the pyridine series of potential chemotherapeutic interest, Morgan and Stewart (*Chem. and Ind.*, 1937, 670) studied the ring closure of picryl-2-aminopyridine. They found that removal of the elements of nitrous acid readily took place on heating in a suitable diluent to give a new base to which they assigned the constitution of a 1 : 3-dinitro-9 : 12-diazafluorene [4 : 6-dinitropyrido(1′ : 2′ : 1 : 2)-benziminazole]. They pointed out in a subsequent communication (*J.*, 1938, 1292) that, although this reaction could theoretically give rise to a dinitro-α-carboline, yet such a formulation was inconsistent with the observations that (*a*) picryl-2-amino-3-methylpyridine, the structure of which precluded the formation of a carboline, behaved in an exactly similar way, and (*b*) reduction followed by deamination gave a new base which was not identical but isomeric with the known α-carboline. Further work showed that picryl chloride could be replaced by the technically available 1-chloro-2 : 4-dinitrobenzene (*J.*, 1939, 1057), provided that somewhat more drastic methods of ring closure were employed.


(I.)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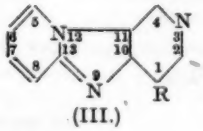
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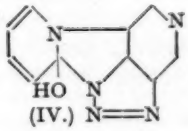
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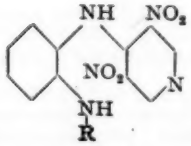
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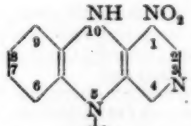
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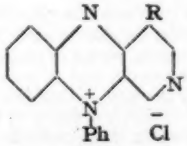
(VII.)

We now find that (I; R = Cl) undergoes ready condensation with 2-aminopyridine in benzene solution in the presence of sodium acetate to give N-(3′ : 5′-*dinitro*-4′-*pyridyl*)-2-*aminopyridine* (II) (shown as the imino-form). Pyrolysis of this compound in quinoline leads to the facile removal of the elements of nitrous acid followed by separation of a new base, $C_{10}H_6O_2N_4$, to which we have assigned the constitution of a 1-*nitro*-3 : 9 : 12-*triazafluorene* (III; R = NO_2). Attempts to confirm this structure by a similar condensation of 2-amino-3-methylpyridine with (I; R = Cl), as used by Morgan and Stewart (1938, *loc. cit.*) in the case of the simpler diazafluorenes, and thus exclude the alternative diazacarbazole formulation for our product, were unsuccessful for reasons outlined below.

Reduction of (III; R = NO_2) gave 1-*amino*-3 : 9 : 12-*triazafluorene* (III; R = NH_2), characterised by an *acetyl* derivative. The latter gave only a *monomethiodide*. The behaviour of (III; R = NH_2) with nitrous acid showed certain points of interest. In acid solution the normal diazonium salt was presumably formed as evidenced by the formation of a red dyestuff on coupling with alkaline 2-naphthol. When an acid solution of the diazonium salt was heated for a few minutes, however, a rearrangement occurred leading to the formation of an isomeric compound, for which we tentatively propose the structure of a 13-*hydroxy*-3 : 12-*diaza*-12 : 13-*dihydrocarbazole*-1 : 9-*diazole* (IV). Our evidence for structure (IV) is the presence in the product of a free hydroxyl group (Zerewitinoff determination) which is evidently of a tertiary character, as the compound was recovered unchanged after prolonged boiling with acetic anhydride.

Attempts to extend the above reactions to 2-amino-3-methylpyridine, 2-aminoquinoline, and 9-aminophenanthridine proved unsuccessful. In contrast to the ready formation of (II), the yellow products in all three cases appeared to be the molecular addition *complexes* of the bases with 3 : 5-dinitro-4-hydroxypyridine (I; R = OH). The same compounds were also obtained by direct addition of (I; R = OH) to boiling solutions of the bases in suitable solvents, although, when prepared in this way, their decomposition points differed slightly from those of the products formed *via* the chloro-compound (I; R = Cl). The bases were regenerated from the complexes by treatment with dilute acetic acid, followed by removal of the insoluble 3 : 5-dinitro-4-hydroxypyridine and basification of the filtrate, or by warming with a slight excess of caustic alkali, in which (I; R = OH) is readily soluble. Thus in properties and appearance these complexes resemble the picrates.

Now Ullmann and Bruck (*Ber.*, 1908, **41**, 3938) have shown that 2 : 4-dinitronaphthyl 1-*p*-toluenesulphonate resembles picryl chloride in its reaction with *o*-aminophenol to give a phenoxazine derivative. We therefore attempted the preparation of 3 : 5-dinitropyridyl 4-*p*-toluenesulphonate (I; R = $O{\cdot}SO_2{\cdot}C_7H_7$) in the hope that the interaction of such a derivative with 2-aminopyridine, for example, would furnish an alternative route to compounds of type (II). When 3 : 5-dinitro-4-hydroxypyridine (I; R = OH) was treated with *p*-toluenesulphonyl chloride in diethylaniline solution on the water-bath, however, a sulphur-free product was obtained giving consistent analytical figures for $C_{10}H_4O_9N_6$. There appears to be little doubt that this compound is the unknown *di-(3 : 5-dinitro-4-pyridyl) ether*, as, in common with the *o*- and *p*-nitrophenyl alkyl ethers, it underwent ready hydrolysis on treatment with alkalis to furnish (I; R = OH). Again, nitroethers such as trinitroanisole can be used like picryl chloride in the synthesis of phenoxazines (Misslin and Bau, *Helv. Chim. Acta*, 1919, **2**, 295). 4-Chloro-3 : 5-dinitropyridine (I; R = Cl) has been shown in earlier communications (Petrow and Rewald, *loc. cit.*) to give 1-nitro-3-azaphenoxazine with *o*-aminophenol, and 1-nitro-3-azaphenthiazine with *o*-aminothiophenol. We now find that di-(3 : 5-dinitro-4-pyridyl) ether can be equally well employed in these reactions. Condensation of the ether with 2-aminopyridine, however, failed to give (II), the product being the addition complex of the base with 3 : 5-dinitro-4-hydroxypyridine (I; R = OH).

Removal of the elements of nitrous acid from the picryl derivatives of *o*-phenylenediamine was first achieved by Kehrmann and Messinger (*Ber.*, 1893, **26**, 2372), who found that picrylmethyl-*o*-phenylenediamine passed smoothly on warming with alkali into *N*-methyldihydrodinitrophenazine, whilst phenylpicryl-*o*-phenylenediamine gave *N*-phenyldihydrodinitrophenazine. The reduction of the latter compound was subsequently investigated by Kehrmann (*Ber.*, 1899, **32**, 2607; cf. Kehrmann and Kramer, *Ber.*, 1900, **33**, 3074) who found that, when alcoholic stannous chloride was employed, *iso*phenosafranine was obtained. The parent compound of the series, dinitrodihydrophenazine, was obtained by Leemann and Grandmougin (*Ber.*, 1908, **41**, 1308; cf. Kehrmann and Messinger, *loc. cit.*) from *o*-phenylenediamine. A further extension of the reaction was made by Kehrmann and Effront (*Helv. Chim. Acta*, 1921, **4**, 517) who showed that 1-chloro-2 : 6-dinitrobenzene could be equally well employed in these reactions.

We successfully condensed 4-chloro-3 : 5-dinitropyridine (I; R = Cl) with *o*-phenylenediamine, obtaining N-*(3 : 5-dinitro-4-pyridyl)-o-phenylenediamine* (V; R = H) in excellent yield, but all attempts at ring closure of this compound failed. Prolonged heating with one molecular proportion of alkali led only to profound decomposition. Pyrolysis in neutral solvents led to the formation of brown amorphous products, a result no doubt connected with the instability of dihydrophenazines in the presence of oxidising agents. In contrast to these results, facile removal of the elements of nitrous acid readily occurred when N-*(3 : 5-dinitro-4-pyridyl)-N'-phenyl-o-phenylenediamine* (V; R = Ph), obtained from phenyl-*o*-phenylenediamine, was heated with one molecular proportion of alkali, giving *1-nitro-5-phenyldihydro-3-azaphenazine* (VI) in 60% yield. Pyrolysis of (V; R = Ph) in boiling quinoline on one occasion gave 65% of (VI), but in general the yields by this method were very low. Reduction of (VI) gave *1-amino-5-phenyl-3-azaphenazonium chloride* (VII; R = NH_2), characterised by its well-defined *acetyl* derivative (VII; R = NHAc). The formation of the phenylaminophenazonium salts by reduction of the *N*-phenylnitrodihydrophenazines is a well-established reaction, *viz.*, the preparation of *iso*phenosafranine referred to above.

Biological examination of 1-amino-3 : 9 : 12-triazafluorene (III; R = NH_2) kindly undertaken at our request by Mr. R. H. Thorpe (Wellcome Physiological Research Laboratories, on behalf of the Therapeutic Research Corporation of Great Britain, Ltd.) has shown that this substance is a convulsant poison. The $L.D._{50}$ for intravenous injection in mice was about 60 mg./kg. In the anæsthetised dog the compound caused a fall in blood pressure equivalent to about 25 mm. of mercury followed by recovery in about three minutes. After the injection of 3 mg./kg. of morphine the blood pressure fell by about 25 mm. and an injection of 5 mg./kg. of (III; R = NH_2) caused a transient increase lasting a minute or so. A further similar dose gave a rise of blood pressure of 40 mm. of mercury, but the duration of the effect was very short. Dr. R. Wien and Dr. J. Harrison (Biological Division, May and Baker Ltd., on behalf of the Therapeutic Research Corporation of Great Britain, Ltd.) have kindly examined 1-amino-5-phenylphenazonium chloride (VII; R = NH_2). The $L.D._{50}$ in mice was 20 mg./kg. for intravenous injections and 25 mg./kg. for subcutaneous injections. The compound was inactive against *Staph. aureus*, *B. coli*, *Ps. aeruginosa* (*pyocyanea*), *T. equiperdum*, and *T. congolense*.

Experimental.

M. ps. are corrected. Microanalyses and Zerewitinoff determination are by Drs. Weiler and Strauss, Oxford.

N-*(3' : 5'-Dinitro-4'-pyridyl)-2-aminopyridine* (II).—3 : 5-Dinitro-4-hydroxypyridine (18·5 g.), phosphorus pentachloride (34 g.), and a little phosphorus oxychloride were heated under reflux for 1 hour at 160°. Excess of phosphorus

halides was removed under reduced pressure on the water-bath, and to the cooled product 2-aminopyridine (15 g.) in dry benzene (*ca.* 40 ml.) was added with shaking. The mixture was warmed gently on the water-bath for 2 minutes, and sodium acetate (12 g.) followed by benzene (100 ml.) added. The mixture was heated for 10 minutes under reflux. The filtrate on cooling deposited *N*-(3′ : 5′-*dinitro*-4′-*pyridyl*)-2-*aminopyridine*, lemon-yellow plates from alcohol, m. p. 184—185° (Found : C, 46·2; H, 2·9; N, 26·7. $C_{10}H_7O_4N_5$ requires C, 46·2; H, 2·7; N, 26·8%). Yield, 5·1 g. (20%).

1-*Nitro*-3 : 9 : 12-*triazafluorene* (III; R = NO_2).—*N*-(3′ : 5′-Dinitro-4′-pyridyl)-2-aminopyridine (5 g.) and redistilled quinoline (10 ml.) were heated under reflux for 10 minutes. Evolution of oxides of nitrogen took place followed by sudden separation of 1-*nitro*-3 : 9 : 12-*triazafluorene*, light yellow needles from nitrobenzene, m. p. 319° (Found : C, 56·3; H, 2·9; N, 26·2. $C_{10}H_6O_2N_4$ requires C, 56·1; H, 2·8; N, 26·2%). Yield, 3 g. (75%).

1-*Acetamido*-3 : 9 : 12-*triazafluorene* (III; R = NHAc).—Finely powdered 1-nitro-3 : 9 : 12-triazafluorene (2 g.), reduced iron (3 g.), ethanol (7 ml.), water (3 ml.), and concentrated hydrochloric acid (0·5 ml.) were heated under reflux for 2 hours. The filtrate and washings were concentrated until crystallisation commenced. The product (1 g.), after two crystallisations from aqueous ethanol (charcoal), was heated under reflux with acetic anhydride (7 ml.) for 30 minutes. 1-*Acetamido*-3 : 9 : 12-*triazafluorene* formed white needles from aqueous ethanol, m. p. 264—265° (Found : C, 63·6; H, 4·4; N, 25·0. $C_{12}H_{10}ON_4$ requires C, 63·7; H, 4·4; N, 24·8%). Yield, 700 mg. (33%). The *methiodide*, prepared from the methosulphate formed by adding methyl sulphate (650 mg.) to a hot solution of the base (1 g.) in nitrobenzene (5 ml.), formed light yellow hexagonal rods from water, m. p. 311° (decomp.) (Found : I, 33·9. $C_{13}H_{13}ON_4I$ requires I, 34·5%).

1-*Amino*-3 : 9 : 12-*triazafluorene* (III; R = NH_2), obtained by heating the acetamido-compound (2 g.) with 2N-hydrochloric acid (50 ml.) for 1½ hours, formed light yellow needles from aqueous methanol, m. p. 256—257° (Found : C, 65·0; H, 4·4; N, 30·0. $C_{10}H_8N_4$ requires C, 65·2; H, 4·4; N, 30·4%).

13-*Hydroxy*-3 : 12-*diaza*-12 : 13-*dihydrocarbazole*-1 : 9-*diazole* (IV).—1-Amino-3 : 9 : 12-triazafluorene (1·8 g.) dissolved in 2N-hydrochloric acid (50 ml.) was gradually treated at −5° with an ice-cold solution of sodium nitrite (800 mg.). After 20 minutes at 0° the solution was boiled for 5 minutes, cooled, made alkaline with sodium hydroxide solution, and the product precipitated by the passage of carbon dioxide. Recrystallisation of the brown powder from aqueous acetic acid gave 13-*hydroxy*-3 : 12-*diaza*-12 : 13-*dihydrocarbazole*-1 : 9-*diazole*, felted white needles, m. p. 314° (decomp.) (Found : C, 56·1; H, 3·2; N, 33·0; active hydrogen (Zerewitinoff), 0·41. $C_{10}H_7ON_5$ requires C, 56·3; H, 3·3; N, 32·9%; active hydrogen, 0·47%).

3 : 5-*Dinitro*-4-*hydroxypyridine Addition Complexes*.—Method (*A*) consisted in treating a boiling solution of the base in benzene or xylene with an equivalent amount of recrystallised 4-chloro-3 : 5-dinitropyridine (cf. Petrow and Rewald, *loc. cit.*) followed by addition of finely powdered anhydrous sodium acetate. After 30 minutes' refluxing the complex was isolated by filtration followed by extraction of the insoluble residues with pyridine or nitrobenzene. Method (*B*) involved the addition of the very finely powdered dinitrohydroxypyridine to a boiling solution of the base in benzene or xylene. After 30 minutes under reflux the mixture was filtered and the *complex* purified by crystallisation from pyridine or spirit.

From 2-aminopyridine : (*B*) gave yellow felted needles, m. p. 224° (Found : C, 43·0; H, 3·3; N, 24·8. $C_{10}H_9O_5N_5$ requires C, 43·0; H, 3·2; N, 25·1%). From 2-amino-3-methylpyridine : (*A*) gave light yellow needles, m. p. 261° (decomp.) (Found : N, 23·6. $C_{11}H_{11}O_5N_5$ requires N, 23·9%). (*B*) gave m. p. 259° (decomp.) (Found : C, 45·1; H, 3·5; N, 23·9. $C_{11}H_{11}O_5N_5$ requires C, 45·0; H, 3·8; N, 23·9%). From 2-aminoquinoline : (*A*) gave light yellow needles, m. p. 269° (decomp.) (Found : C, 51·1; H, 3·3; N, 21·5. $C_{14}H_{11}O_5N_5$ requires C, 51·1; H, 3·3; N, 21·3%). (*B*) gave m. p. 269° (decomp.) (Found : N, 21·7%). From 9-aminophenanthridine : (*A*) gave light yellow needles, m. p. 259—260° (Found : C, 56·8; H, 3·6; N, 18·2. $C_{18}H_{13}O_5N_5$ requires C, 57·0; H, 3·4; N, 18·5%). (*B*) gave m. p. 267° (Found : N, 18·7%). Complexes prepared by the two methods gave no depression of m. ps. in admixture.

Di-(3 : 5-*dinitro*-4-*pyridyl*) *Ether*.—Finely powdered 3 : 5-dinitro-4-hydroxypyridine (2 g.) and *p*-toluenesulphonyl chloride (2 g.) suspended in redistilled diethylaniline (8 ml.) were warmed on the water-bath for 10 minutes. Spirit (30 ml.) was immediately added and, after allowing to cool, the brown crystalline powder collected and crystallised from ethanol–acetone. *Di*-(3 : 5-*dinitro*-4-*pyridyl*) *ether* formed light brown needles, m. p. 288° (decomp.) (Found : C, 34·3; H, 1·2; N, 24·0. $C_{10}H_4O_9N_6$ requires C, 34·1; H, 1·1; N, 23·9%). Yield, 1·5 g. (80%). When the ether was hydrolysed by heating under reflux with aqueous sodium hydroxide, followed by precipitation with acetic acid and crystallisation from hot water, characteristic plates of 3 : 5-dinitro-4-hydroxypyridine were obtained (Found : N, 22·7. Calc. for $C_5H_3O_5N_3$: N, 22·8%).

5-*Nitro*-3-*azaphenoxazine*.—Di-(3 : 5-dinitro-4-pyridyl) ether (1 g.) and *o*-aminophenol (1 g.) in spirit (20 ml.) were heated under reflux for 10 minutes. Excess of ammonia (*d*, 0·880) was then added and the heating continued for a further 20 minutes. After allowing to cool, the 5-nitro-3-azaphenoxazine was collected. It formed deep red crystals, m. p. 209—210° (Found : N, 18·8. Calc. for $C_{11}H_7O_3N_3$: N, 18·3%), not depressed in admixture with an authentic specimen (Part III, *loc. cit.*).

5-*Nitro*-3-*azaphenthiazine*.—Di-(3 : 5-dinitro-4-pyridyl) ether (1·5 g.) and *o*-aminothiophenol zinc double salt (1·5 g.), suspended in ethanol (30 ml.), were treated with concentrated sulphuric acid (1 ml.). The mixture was heated under reflux until evolution of oxides of nitrogen had ceased (*ca.* 1½ hours). The resulting solution was treated at the boiling point with 33% aqueous sodium hydroxide solution until the appearance of a permanent purple coloration, and then poured into water (200 ml.). On cooling, the product was collected and crystallised from ethanol. 5-Nitro-3-azaphenthiazine formed purple plates, m. p. 143—144° (Found : N, 17·5. Calc. for $C_{11}H_7O_3N_3S$: N, 17·1%), not depressed in admixture with an authentic specimen (Part IV, *loc. cit.*).

N-(3 : 5-*Dinitro*-4-*pyridyl*)-*o*-*phenylenediamine* (V; R = H).—Recrystallised 4-chloro-3 : 5-dinitropyridine, prepared from (I; R = OH; 10 g.), was added to *o*-phenylenediamine (2 g.) and anhydrous sodium acetate (5 g.) in boiling benzene (70 ml.). After 30 minutes under reflux the mixture was cooled and the solids were collected and thoroughly extracted with boiling water and cold dilute aqueous sodium hydroxide solution. *N*-(3 : 5-*Dinitro*-4-*pyridyl*)-*o*-*phenylenediamine* formed red hexagonal plates from aqueous pyridine, m. p. 222° (decomp.) (Found : C, 48·6; H, 3·4; N, 25·4. $C_{11}H_9O_4N_5$ requires C, 48·0; H, 3·3; N, 25·4%). Yield, 4·3 g. (85%).

N-(3 : 5-*Dinitro*-4-*pyridyl*)-*N*′-*phenyl*-*o*-*phenylenediamine* (V; R = Ph).—Recrystallised 4-chloro-3 : 5-dinitropyridine (*ca.* 6 g., prepared from 18·5 g. of the hydroxy-compound) was added to boiling phenyl-*o*-phenylenediamine (7·2 g.) anhydrous sodium acetate (10 g.), and benzene (100 ml.). After 15 minutes the hot mixture was filtered. *N*-(3 : 5-*Dinitro*-4-*pyridyl*)-*N*′-*phenyl*-*o*-*phenylenediamine* separated on cooling; bright red prisms from ethanol, m. p. 180—182° (decomp.) (Found : C, 58·0; H, 3·9; N, 20·0. $C_{17}H_{13}O_4N_5$ requires C, 58·1; H, 3·7; N, 19·9%). Yield, 9 g. (66%).

1-*Nitro*-5-*phenyl*-5 : 10-*dihydro*-3-*azaphenazine* (VI).—(a) *N*-(3 : 5-Dinitro-4-pyridyl)-*N*′-phenyl-*o*-phenylenediamine (3 g.) and redistilled quinoline (9 ml.) were heated under reflux for 5 minutes. Oxides of nitrogen were evolved. The quinoline was removed in steam and the solid crystalline residue crystallised from benzene. 1-*Nitro*-5-*phenyl*-5 : 10-*dihydro*-3-*azaphenazine* formed dark violet prisms, m. p. 247—247·5° (Found : C, 67·0; H, 4·2; N, 18·3. $C_{17}H_{12}O_2N_4$ requires C, 67·1; H, 4·0; N, 18·4%). Yield, 1·7 g. (65%). (b) To a boiling suspension of finely powdered *N*-(3 : 5-dinitro-4-pyridyl)-*N*′-phenyl-*o*-phenylenediamine (2 g.) in ethanol (75 ml.) an ethanolic solution of potassium hydroxide

(300 mg.) was slowly added and the heating continued for a further 2 hours. After allowing to cool, the product was collected and crystallised from benzene, m. p. 247—247·5° (Found: N, 18·0), not depressed in admixture with the compound obtained by method (a). Yield, 1 g. (60%).

1-*Amino-5-phenyl-3-azaphenazonium Chloride* (VII; R = NH_2).—Finely powdered 1-nitro-5-phenyl-5 : 10-dihydro-3-azaphenazine (2 g.), reduced iron (5 g.), methanol (15 ml.), water (4 ml.), and ferric chloride (3 g.) were heated under reflux for 1¼ hours. On concentration of the filtrate and washings 1-*amino-5-phenyl-3-azaphenazonium chloride* separated; bronze plates from methanol, m. p. >310° (Found: C, 66·1; H, 4·7; N, 18·5; Cl, 11·8. $C_{17}H_{13}N_4Cl$ requires C, 66·1; H, 4·2; N, 18·2; Cl, 11·5%). Yield, 1 g. (44%).

1-*Acetamido-5-phenyl-3-azaphenazonium chloride* (VII; R = NHAc), red prisms, m. p. 275° (decomp.) (Found: C, 65·1; H, 4·7; N, 16·3; Cl, 10·1. $C_{19}H_{15}ON_4Cl$ requires C, 65·0; H, 4·3; N, 16·0; Cl, 10·1%), was prepared by heating the amino-compound (1 g.) with acetic anhydride (10 ml.) for 15 minutes under reflux. After allowing to cool the purple solids were collected and crystallised (charcoal) from ethanol.

The authors thank the Therapeutic Research Corporation of Great Britain Limited for grants and for certain facilities. The major portion of this work was done in the period when Queen Mary College was at Cambridge, and the authors acknowledge with gratitude the laboratory facilities placed at their disposal by the University of Cambridge.

QUEEN MARY COLLEGE (UNIVERSITY OF LONDON), E. 1. [*Received, January 10th*, 1946.]

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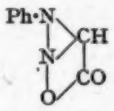
118. *The Sydnones. A New Class of Compound containing Two Adjacent Nitrogen Atoms.*

By RONALD A. EADE and J. CAMPBELL EARL.

Several analogues of the substance previously obtained by the action of acetic anhydride on *N*-nitrosophenylglycine have been prepared and studied. These substances all yield the corresponding hydrazines on decomposition with hydrochloric acid. Their molecular structure is still in doubt and they are therefore referred to as "sydnones". They are crystalline, relatively stable compounds and offer some promise as reagents in view of the ease with which the hydrazines can be generated from them.

IN an earlier communication (Earl and Mackney, *J.*, 1935, 899) a crystalline product formed by the action of acetic anhydride on *N*-nitrosophenylglycine was described. The structure assigned to the substance after a study of its decomposition with acid and alkaline reagents was that of a lactone of 2-hydroxy-1-phenyldiaziridine-3-carboxylic acid:



There is at present no further evidence for or against this structure. It is, however, of such an unusual type that it cannot be finally accepted without a deeper consideration of the stereochemical and other factors involved. It is proposed in the meantime to refer to substances of this type as "sydnones," the example given above being *N*-phenylsydnone.

Before undertaking a detailed structural study, we have prepared several other sydnones. In general, the *N*-nitrosoarylglycines pass more or less readily into the corresponding sydnones when treated with acetic anhydride. Exposure to sunlight was found to affect the reaction adversely, especially with the *o*- and *p*-nitrophenyl derivatives. All the products were crystalline, white or pale yellow, and soluble in hot benzene and hot alcohol (except *p*-nitrophenylsydnone), but not very soluble in the cold.

Decomposition of the crystalline products by heating with hydrochloric acid gave carbon dioxide and the substituted phenylhydrazines. A large excess of acid sometimes brought about a further decomposition of the hydrazine (*e.g.*, *p*-ethoxyphenylhydrazine) and only 50% excess was used in such cases, the hydrazine being brought into reaction with *p*-nitrobenzaldehyde as soon as possible. The relative stability of the sydnones, compared with the free hydrazines or their salts, suggests that they may be useful reagents for the characterisation of carbonyl compounds, since a solution of the corresponding hydrazine salt can be so quickly prepared from them.

EXPERIMENTAL.

Preparation of the Glycine Ethyl Esters.—General method. The amine (M/2), ethyl chloro- or bromo-acetate (M/2), and sodium acetate crystals (M/2), together with a small amount of alcohol, were heated in an oil-bath at 120—125° for 5 hours under reflux. The reaction mixture was poured into water, made strongly acid with hydrochloric acid, and extracted with ether to remove non-basic substances. The solution was then cooled to 0—5° and neutralised with 20% sodium hydroxide solution. The glycine ethyl ester was extracted with ether and purified either by fractional distillation under reduced pressure, or, if a solid of high m. p., by recrystallisation from a suitable solvent.

o-*Methoxyphenylglycine ethyl ester.* The crude ester was prepared by Diepholder (*Ber.*, 1899, **32**, 3518). The present preparation, using ethyl chloroacetate, gave 52 g. of purified ester (50%), a colourless oil rapidly darkening in air; b. p. 177—178°/15 mm. The p-*nitrobenzoyl* derivative, recrystallised from alcohol, had m. p. 123° (Found: C, 60·20; H, 5·05. $C_{18}H_{18}O_6N_2$ requires C, 60·30; H, 5·06%).

o-*Ethoxyphenylglycine ethyl ester.* This ester was mentioned by Vater (*J. pr. Chem.*, 1884, **29**, 295) who obtained it as a solid but did not give its m. p. or b. p. Using ethyl chloroacetate, 49 g. (44%) of ester were obtained; b. p. 183—184°/18 mm. The p-*nitrobenzoyl* derivative, recrystallised from alcohol, had m. p. 127° (Found: C, 61·22; H, 5·47. $C_{19}H_{20}O_6N_2$ requires C, 61·28; H, 5·43%).

m-*Methoxyphenylglycine ethyl ester.* *m*-Anisidine was prepared by reducing *m*-nitroanisole with hydrogen at atmospheric pressure using Raney nickel as a catalyst. From *m*-anisidine and ethyl bromoacetate, 61 g. of crude *ester*, m. p. 36—37°, were obtained. On redistilling, this gave 51 g. (49%), m. p. 39—40°, b. p. 199°/24 mm. (Found: C, 63·10; H, 7·26. $C_{11}H_{15}O_3N$ requires C, 63·15; H, 7·23%). The *p-nitrobenzoyl* derivative, recrystallised from alcohol, had m. p. 130—131° (Found: C, 60·11; H, 5·09. $C_{18}H_{18}O_6N_2$ requires C, 60·30; H, 5·06%).

m-*Nitrophenylglycine ethyl ester.* Previously prepared by Deutsch (*J. pr. Chem.*, 1907, **76**, 353) from methyl chloroacetate and *m*-nitroaniline. A purer product was prepared using ethyl bromoacetate. The crude ester was precipitated by pouring the reaction mixture with stirring into 1% hydrochloric acid (400 ml.), then ground with more 1% hydrochloric acid (400 ml.), washed with water and dried in a vacuum. 13·5 G. of *m*-nitroaniline were recovered by neutralising the acid filtrates. The crude ester (86 g.; m. p. 81—83°) was recrystallised twice from alcohol, giving 71 g. (63%), m. p. 86—87°. Further repeated recrystallisation raised the m. p. to 87—88°. The highest m. p. previously recorded was 84° (Deutsch, *loc. cit.*) (Found: C, 53·46; H, 5·31. Calc. for $C_{10}H_{12}O_4N_2$: C, 53·57; H, 5·39%).

β-Naphthylglycine ethyl ester (cf. Bischoff and Hausdorfer, *Ber.*, 1892, **25**, 2296). The crude product was purified by melting it under water, followed by two crystallisations from alcohol. Yield of purified ester after 20 hours' heating of the reaction mixture was 40 g. (34%), m. p. 87°.

Hydrolysis of the Esters.—The esters were hydrolysed by refluxing with 50% excess of sodium hydroxide solution (10%) containing 10% of alcohol for several minutes after complete solution had been effected. Hydrolysis was usually complete in 5 to 10 minutes and in some cases the reaction was very vigorous. The solution was neutralised to Congo red with hydrochloric acid, and the precipitated glycine was filtered off, washed, and dried in a vacuum. The product was usually pure enough for nitrosation without further purification. In the hydrolysis of *m*-methoxyphenylglycine ethyl ester the alcohol was omitted as the glycine was appreciably soluble in aqueous alcohol.

m-*Methoxyphenylglycine* separated as an oil on neutralising the hydrolysis mixture and crystallised on standing; m. p. 65—66°. Recrystallisation from hot water gave colourless crystals of the same m. p. containing water of crystallisation, removed by drying at 78°/2 mm.; m. p. of the anhydrous substance, 85—86° (Found: C, 59·43; H, 6·23; N, 7·83. $C_9H_{11}O_3N$ requires C, 59·65; H, 6·12; N, 7·77%).

Direct Preparation of Glycines.—The following glycines were prepared directly from chloro- or bromo-acetic acid by published methods: *p*-methoxyphenyl- (Vater, *J. pr. Chem.*, 1884, **29**, 294); *o*-nitrophenyl- (Plöchl, *Ber.*, 1886, **19**, 7); *p*-nitrophenyl- (G.P. 88,433; Friedländer, **4**, 1156); α-naphthyl- (Jolles, *Ber.*, 1889, **22**, 2372).

By increasing the ratio of *o*-nitroaniline to bromoacetic acid, the yield of *o*-nitrophenylglycine was raised from 42 to 80% (based on the amount of bromoacetic acid taken). It was not found possible to raise the m. p. of α-naphthylglycine above 192°, compared with 198—199° recorded by Bischoff and Nastvogel (*Ber.*, 1889, **22**, 1808). A sample prepared from the ethyl ester also had m. p. 192°.

Nitrosation of the Glycines.—Some of the nitroso-compounds, especially those with *o*-substituents, were changed on exposure to light. The nitrosations were therefore carried out in the absence of direct sunlight. The nitroso-compounds were usually recrystallised, but, when too unstable, the crude products were used directly for the next stage. The method of nitrosation varied according to the glycine being treated.

N-*Nitroso*-N-(o-*methoxyphenyl*)*glycine.* The glycine (M/10) was dissolved in a mixture of 10N-HCl (16 ml.) and water (80 ml.). The solution was cooled to 0° and a slight excess of sodium nitrite (7·1 g.) in water (20 ml.) added with stirring during ½ hour. The *nitroso* compound commenced to precipitate in the first few minutes. After another 1½ hours' stirring at 0°, the nitroso-compound was filtered off and washed successively with 5% hydrochloric acid and water. The crude product (a buff powder, changing colour on keeping) was dried in a vacuum over sodium hydroxide. Yield, 95%; m. p. 76—78° (decomp.). After being crystallised several times from aqueous alcohol, the compound had m. p. 82—83° (decomp.) (Found: N, 12·8. $C_9H_{10}O_4N_2$ requires N, 13·3%).

N-*Nitroso*-N-(o-*ethoxyphenyl*)*glycine* was prepared similarly to the *o*-methoxy compound. Yield of crude product, 85%; m. p. 89—90° (decomp.). After recrystallisation from aqueous alcohol the compound had m. p. 94·5—95·5° (decomp.) (Found: N, 12·2. $C_{10}H_{12}O_4N_2$ requires N, 12·5%).

N-*Nitroso*-N-(p-*methoxyphenyl*)*glycine* was also prepared similarly to the *o*-methoxy compound. Yield of crude product, 91%; m. p. 120·5° (decomp.). Recrystallisation from aqueous alcohol raised the m. p. to 121·5° (decomp.) (Found: N, 13·2. $C_9H_{10}O_4N_2$ requires N, 13·3%).

N-*Nitroso*-N-(m-*methoxyphenyl*)*glycine* was prepared by the method used by Earl and Mackney for *N*-nitrosophenylglycine (*loc. cit.*). Yield of crude product, 90%; m. p. 89—91° (decomp.). After purification by dissolving in dilute sodium hydroxide, treating with charcoal and regenerating with acid, it had m. p. 92—93° (decomp.) (Found: C, 51·56; H, 4·82. $C_9H_{10}O_4N_2$ requires C, 51·42; H, 4·79%).

N-*Nitroso*-N-(m-*nitrophenyl*)*glycine* was also prepared by the method of Earl and Mackney, and recrystallised from aqueous alcohol. Yield of purified product, 76%; m. p. 160—161° (decomp.) (Found: C, 42·69; H, 3·20. $C_8H_7O_5N_3$ requires C, 42·65; H, 3·13%).

N-*Nitroso*-N-(o-*nitrophenyl*)*glycine.* The glycine (50 g.) was dissolved in 36N-H_2SO_4 (350 ml.) by gentle warming. The solution was cooled to 0° and finely powdered sodium nitrite (19 g.) added during ½ hour with vigorous stirring After another 1½ hours at 0°, with continued stirring, the solution was poured on crushed ice. The viscous product soon solidified, and was filtered off, washed by grinding with water, and dried in a vacuum. Yield, 49·5 g., m. p. 107—108° (decomp.). The *product* was too unstable to be recrystallised from a solvent, but was purified by treating it with excess of saturated sodium bicarbonate solution, filtering off insoluble material, and acidifying the filtered solution. Yield 48 g.; m. p. 112—113° (decomp.) (Found: N, 18·12. $C_8H_7O_5N_3$ requires N, 18·65%).

N-*Nitroso*-N-(p-*nitrophenyl*)*glycine* was prepared similarly to the *o*-nitrophenyl compound. Crude yield 51 g.; m. p. 143—144° (decomp.). After two recrystallisations from aqueous alcohol 47·2 g. were recovered, m. p. 147·5° (decomp.) (Found: N, 18·9. $C_8H_7O_5N_3$ requires N, 18·65%).

Action of Acetic Anhydride on the Nitroso-compounds. Formation of the Sydnones.—General method. The nitrosoglycine (M/10) was mixed with acetic anhydride (90 ml.), out of direct sunlight. The nitroso compound sometimes dissolved in a few minutes, sometimes after some hours. After 1 to 4 days, the reaction product had sometimes partly separated. The mixture was poured into water (600 ml.) and the excess of acetic anhydride allowed to hydrolyse, after which ammonia or sodium bicarbonate solution was added until the mixture was slightly alkaline. The crude product was filtered off and purified by crystallisation from water or alcohol.

o-*Methoxyphenylsydnone.* Reaction time, 24 hours. Crude yield, 13·8 g.; m. p. 84—86° (decomp.). Recrystallised several times from alcohol, with decolorising charcoal, the purified *product* (6·5 g.), had m. p. 96·5—97·5° (Found: C, 56·17; H, 4·16; N, 14·62. $C_9H_8O_3N_2$ requires C, 56·24; H, 4·19; N, 14·58%).

m-*Methoxyphenylsydnone.* Reaction time, 48 hours. Crude yield, 17·7 g.; m. p. 136·5—137·5°. Recrystallisation did not raise the m. p. of the *compound* (Found: C, 56·42; H, 4·17; N, 14·62%).

p-*Methoxyphenylsydnone.* Reaction time, 24 hours. Crude yield, 17·7 g.; m. p. 124—125° (decomp.). Recrystallisation from alcohol gave 14·7 g. of the *compound*, m. p. 125—126° (decomp.) (Found: C, 56·26; H, 4·18; N, 14·56%).

o-*Ethoxyphenylsydnone.* Reaction time, 48 hours. Crude yield, 17·1 g.; m. p. 96—97° (decomp.). Recrystallis-

ation from aqueous alcohol gave 13·5 g. of the *compound*, m. p. 102° (decomp.) (Found: C, 58·00; H, 4·84; N, 13·63. $C_{10}H_{10}O_3N_2$ requires C, 58·23; H, 4·89; N, 13·59%).

β-Naphthylsydnone. Reaction time 4 days (using *N*-nitroso-*N*-β-naphthylglycine prepared according to Jolles, *loc. cit.*). Crude yield, 18·8 g.; m. p. 141—143°. Recrystallisation from alcohol gave 13·0 g. of the *compound*, m. p. 159° (decomp.) (Found: C, 67·90; H, 3·81; N, 13·23. $C_{12}H_8O_2N_2$ requires C, 67·89; H, 3·81; N, 13·21%). On acidifying the alkaline filtrate 0·5 g. of unchanged nitroso-compound was recovered.

o-*Nitrophenylsydnone*. The crude nitrosoglycine (45 g., M/5) was mixed with acetic anhydride (180 ml.) in which it dissolved completely in 1 hour. After standing for 14 days, the mixture was poured into water (1300 ml.). The dilute acetic acid solution was decanted off and the residual viscous mass warmed with dilute acetic acid which was decanted off. The combined acid solutions on the addition of ammonia gave 2·6 g. of a light yellow solid, m. p. 141—142° (decomp.). Two recrystallisations from alcohol gave 1·9 g. of the *compound*, m. p. 147·5° (Found: C, 46·43; H, 2·46; N, 20·30. $C_8H_5O_4N_3$ requires C, 46·39; H, 2·43; N, 20·27%).

m-*Nitrophenylsydnone*. The nitrosoglycine (22·5 g. M/10) was treated with a mixture of acetic anhydride (90 ml.) and acetic acid (45 ml.). After 30 days the nitroso-compound had completely dissolved and after another 30 days the crude product was isolated and washed well with a solution of sodium bicarbonate. Crude yield 18·1 g.; m. p. 112—115°, still giving a Liebermann nitroso test. Four recrystallisations from alcohol yielded 6·4 g. of the *compound*, m. p. 139—140° (decomp.) (Found: C, 46·41; H, 2·40; N, 20·01. $C_8H_5O_4N_3$ requires C, 46·39; H, 2·43; N, 20·27%).

p-*Nitrophenylsydnone*. The nitrosoglycine (22·5 g. M/10) was mixed with acetic anhydride (90 ml.). After 4 days it was completely dissolved and after six days a precipitate began to form. After 14 days the precipitate was filtered off, washed with acetic anhydride, and dried in a vacuum. Crude yield, 7·4 g.; m. p. 178—179° (decomp.). Two recrystallisations from butyl acetate yielded 5·2 g. of the *compound*, m. p. 187—188° (decomp.) (Found: C, 46·42; H, 2·47; N, 20·21. $C_8H_5O_4N_3$ requires C, 46·39; H, 2·43; N, 20·27%). Pouring the acetic anhydride solution into water gave a mixture of substances from which nothing definite was isolated.

Acid Hydrolysis of the Sydnones.—The sydnone (M/200), water (5 ml.), alcohol (5 ml.), and 10N-HCl (5 ml.) were heated in a boiling water-bath. A vigorous evolution of carbon dioxide took place and the reaction was completed in about 10 minutes, the hydrazine hydrochloride often crystallising out. After concentration to 5—10 ml. the solution was cooled and the hydrochloride filtered off.

o-*Nitrophenylhydrazine*. Yield, 0·8 g. (90%); m. p. (rapid heating) 200—201° (decomp.). The hydrochloride was converted into benzaldehyde *o*-nitrophenylhydrazone, m. p. 191·5° (Gastaldi, *Gazzetta*, 1912, **42**, 616, records m. p. 187°).

m-*Nitrophenylhydrazine*. Yield 0·8 g. (90%); m. p. 195—197° (decomp.). Benzaldehyde *m*-nitrophenylhydrazone was prepared, m. p. 130° (Van Ekenstein and Blanksma, *Rec. Trav. chim.*, 1905, **24**, 36, record m. p. 130°).

p-*Nitrophenylhydrazine*. The hydrochloride was not isolated. Benzaldehyde *p*-nitrophenylhydrazone (1·1 g.) was prepared, m. p. 190—191° (Ciusa and Vecchiotti, *Gazzetta*, 1912, **42**, 529, record m. p. 195—196°).

β-Naphthylhydrazine. Yield 0·85 g. (92%); m. p. 240° (decomp.). Benzaldehyde β-naphthylhydrazone, m. p. 191° (Fichter and Fröhlich, *Chem. Zentr.*, 1903, II, 427, record m. p. 194°).

Hydrolysis of the Alkoxyphenylsydnones.—Milder conditions were necessary for this group of sydnones. The sydnone (M/200), alcohol (6 ml.), and 10N-HCl (0·75 ml., 50% excess) were refluxed for 25 minutes, the solution darkening considerably. Water was added to precipitate any unchanged sydnone, which was filtered off. To the filtrate an aqueous alcoholic solution of *p*-nitrobenzaldehyde (0·7 g.) and excess of sodium acetate were added. The hydrazone was finally precipitated with water and recrystallised from alcohol. p-*Nitrobenzaldehyde* o-*methoxyphenylhydrazone* had m. p. 160° (Found: N, 15·47. $C_{14}H_{13}O_3N_3$ requires N, 15·49%). p-*Nitrobenzaldehyde* m-*methoxyphenylhydrazone* had m. p. 153·5—154·5° (Found: N, 15·47%). p-*Nitrobenzaldehyde* p-*methoxyphenylhydrazone* had m. p. 176·5—177·5° (Found: C, 61·80; H, 4·87. $C_{14}H_{13}O_3N_3$ requires C, 61·96; H, 4·83%). p-*Nitrobenzaldehyde* o-*ethoxyphenylhydrazone* had m. p. 134—135° (Found: C, 63·20; H, 5·33. $C_{15}H_{15}O_3N_3$ requires C, 63·18; H, 5·30%).

The authors thank Miss J. Fildes for performing the many semimicro- and micro-analyses involved and Mr. W. S. Chapman for assistance with the experimental work.

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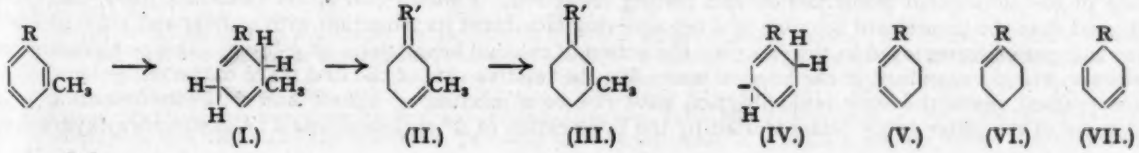
119. *Reduction by Dissolving Metals. Part III.*

By ARTHUR J. BIRCH.

The reduction by sodium and alcohol in liquid ammonia of methoxyalkylbenzenes (Part I, *J.*, 1944, 430) has been further examined, and the reaction extended to dimethylaminoalkylbenzenes. Confirmation of the initial formation of αδ-dihydro-derivatives has been obtained by preparation of derivatives of the βγ-unsaturated ketones produced in the first stage of acid hydrolysis, and in several cases by isolation of the ketones themselves. Further action of sodium in liquid ammonia on the dihydro-compounds gave in many cases small yields of tetrahydro-compounds, hydrolysed by acid to alkyl*cyclo*hexanones. The dihydrotolyl methyl ethers gave in addition a hydrocarbon fraction containing methyl-Δ^1-*cyclo*hexene. The combined processes gave results similar to, but not always identical with, those obtained by the action of calcium hexammine on the aromatic compounds (see table) and the mechanisms are probably similar. The latter reagent produced the same dimethyl*cyclo*hexene from *m*-xylene and 2 : 5-dihydro-*m*-xylene, and reduced *o*-chloro- and *p*-bromo-anisole to a mixture of anisole and 2 : 5-dihydroanisole.

IN Part I (*loc. cit.*) the reduction of methoxyalkylbenzenes with sodium and alcohol in liquid ammonia was assumed to give the αδ-dihydro-derivatives (*e.g.*, I, R = OMe) by analogy with the alkylbenzenes and because of the small ultra-violet absorption in the region 2300—2700 A. of dihydro-*m*-tolyl methyl ether, despite the formation of αβ-unsaturated ketones (*e.g.*, III, R′ = O) by refluxing with dilute mineral acid.



(I.) (II.) (III.) (IV.) (V.) (VI.) (VII.)

This is confirmed by the preparation of the initial βγ-unsaturated ketones (*e.g.*, II, R′ = O) and their derivatives formed from the reduction products of both dimethylamino- and methoxy-alkylbenzenes. The latter (*e.g.*, I, R = OMe) on treatment with cold aqueous sodium bisulphite gave solid derivatives which were decomposed with sodium carbonate to give the ketones themselves; *e.g.*, dihydro-*m*-tolyl methyl ether (I, R = OMe) gave 3-*methyl*-Δ³-cyclo*hexenone* (II, R′ = O). The βγ-unsaturated 2 : 4-dinitrophenylhydrazones [*e.g.*, II, R′ = N·NH·$C_6H_3(NO_2)_2$] were obtained by the action of 2 : 4-dinitrophenylhydrazine sulphate in cold alcohol on the ketones or the dihydro-compounds. Their constitution was confirmed by their light absorption ($\lambda_{max.}$ *ca.* 3680 A.) which resembles that of the saturated ($\lambda_{max.}$ *ca.* 3660 A.) rather than the αβ-unsaturated ketone derivatives ($\lambda_{max.}$ 3830 A.) (cf. Braude and Jones, *J.*, 1945, 498). Similarly, the βγ-unsaturated semicarbazones, obtained by the action of semicarbazide acetate on the ketones or the dihydro-amines, resemble in their absorption ($\lambda_{max.}$ *ca.* 2280 A.) the derivatives of the saturated ketones ($\lambda_{max.}$ *ca.* 2290 A.) rather than those of the αβ-unsaturated ketones ($\lambda_{max.}$ *ca.* 2670 A.) (cf. Evans and Gillam, *J.*, 1943, 568).

It is probable that several of the ketones prepared in Part I contained some of the βγ-unsaturated compounds, since their 2 : 4-dinitrophenylhydrazones melted somewhat below the values now found, and in the case of *p*-tolyl methyl ether it appears from the absorption of the semicarbazone ($\lambda_{max.}$ 2300 A.) that the ketone was the relatively acid-stable 4-methyl-Δ³-*cyclo*hexenone despite the formation of the αβ-unsaturated 2 : 4-dinitrophenylhydrazone, since the latter was prepared in hot acid solution.

The dimethylaminoalkylbenzenes showed the same orientation for hydrogen addition as the corresponding methoxy-compounds since they gave rise to the same derivatives on hydrolysis, and from the dimethyltoluidines the process represents a practical method of obtaining the ketones (αβ-unsaturated with the *ortho*- and *meta*-, βγ-unsaturated with the *para*-) in 55—65% yield free from the acid-soluble starting material. Dimethylamine was also produced in the hydrolysis.

Further reduction of some of the methoxy- and dimethylamino-dihydroalkylbenzenes to the enol derivatives of the alkyl*cyclo*hexanones (*e.g.*, VI, R = OMe, NMe_2) was produced by the action of sodium in liquid ammonia, since, after acid hydrolysis of the product, derivatives of these ketones could be prepared in small yield. Other products of the reaction have not yet been fully investigated, but the tolyl methyl ethers gave considerable amounts of hydrocarbon containing methyl-Δ¹-*cyclo*hexene. Even after the extended reduction, ketonic derivatives corresponding only to the dihydro-derivatives were obtained from a number of compounds (see table). There appear to be two possible explanations of this extended reduction process. The dihydro-derivatives may be isomerised by the sodium through an anion such as (IV) to a conjugated diene (V) which is then reduced to (VI). Double-bond shift in the alternative direction with formation of *cyclo*hexadiene derivatives (VII) may explain the formation of hydrocarbons, since such compounds may well undergo hydrogenolysis and further reduction (cf. Part I, *loc. cit.*; Part II, *J.*, 1945, 809). Alternatively, the tetrahydro-derivatives may actually have been formed in small quantity during the reduction to dihydro-derivatives, the latter then being removed preferentially by further action of sodium with formation of hydrocarbons; however, no derivatives of the saturated ketones have yet been prepared from the dihydro-derivatives.

It is evident that in the preparation of dihydro-derivatives an excess of sodium over the hydrogen donor must be avoided, and by the method now employed it is possible to obtain about 70% yield of product with the tolyl methyl ethers, containing about 95% of dihydro-derivative with the *meta*- and *para*- and 45% with the *ortho*-. The hydrocarbon obtained from *m*-tolyl methyl ether in Part I was undoubtedly due to the method of adding the substance and alcohol to excess of sodium in ammonia, and was not, as at first thought, a primary reduction product.

Kazanskii *et al.* (*J. Gen. Chem. U.S.S.R.*, 1938, **8**, 642; *Bull. Acad. Sci., U.R.S.S.*, 1938, 1061, 1065) explained the reduction of benzenoid hydrocarbons to tetrahydro-derivatives with calcium hexammine by assuming the formation of αδ-dihydro-derivatives, isomerisation of these to conjugated compounds, and further reduction. Since this represents a combination of the two processes outlined above, the products from the second sodium reduction were compared with those obtained by the action of calcium hexammine on the aromatic compounds. The ketonic products obtained on acid hydrolysis were in many cases the same (see table) and any difference can be explained by assuming that the isomerising action of the reagent on the dihydro-derivatives is less powerful than that of sodium. This seems confirmed by the fact that these, when formed, have unconjugated double bonds, since βγ-unsaturated ketonic derivatives could be obtained. Owing to losses of volatile hydrocarbons in the ammonia evolved and the ether used as a solvent, it has been possible to confirm their presence only in the case of *m*-tolyl methyl ether, where methyl-Δ¹-*cyclo*hexene was obtained. As additional evidence for the correctness of Kazanskii's theory it was found that 2 : 5-dihydro-*m*-xylene, obtained by sodium reduction, was further reduced by calcium hexammine to a 1 : 3-dimethyl*cyclo*hexene identical with that obtained by direct reduction of *m*-xylene.

The frequent isolation of tetrahydro- rather than dihydro-derivatives with calcium hexammine is undoubtedly due to the slowness in these cases of the initial addition of two hydrogen atoms compared with the rate of the subsequent isomerisation and further reduction. Einhorn and Ehret (*Annalen*, 1897, **295**, 175) showed that the presence of bromine in a benzene ring facilitated its reduction with sodium and amyl alcohol, the halogen being removed in the process; the action of calcium hexammine on *p*-bromo- and *o*-chloro-anisole was accordingly examined in the hope of increasing the relative rate of the first stage of the reduction. This was realised, since the very rapid reaction gave rise to a mixture of anisole and 2 : 5-dihydroanisole, the presence of the latter being demonstrated by the preparation of Δ³-cyclo*hexenone* 2 : 4-*dinitrophenylhydrazone*.

With anisole itself reduction was slow, and only derivatives of *cyclo*hexanone could be obtained from the product.

In the following table the number of hydrogen atoms added refers only to products of type (I) and (VI), since they are based on an examination of the ketonic products of hydrolysis.

Method A. Reduction with sodium and excess alcohol in ammonia.
Method B. Reduction as in (A) followed by the action of sodium in ammonia.
Method C. Reduction of a solution in ether with calcium hexammine.

Compound.	Number of hydrogen atoms added. A.	B.	C.	Compound.	Number of hydrogen atoms added. A.	B.	C.
Anisole	2	4	4	Dimethylaniline	2	4	4, 2
o-Tolyl methyl ether	2	4	2	Dimethyl-*o*-toluidine	2	4, 2	4, 2
m-Tolyl methyl ether	2	4, 2	2	Dimethyl-*m*-toluidine	2	2	2
p-Tolyl methyl ether	2	4	4	Dimethyl-*p*-toluidine	2	4	4
2 : 4-Dimethylanisole	2	2	2	Dimethyl-*p*-cumidine	2	—	—*
6-Methoxy-1 : 2 : 3 : 4-tetrahydronaphthalene	2	2	2				

Experimental.

Method A.—The substance (7 g.) and ethyl alcohol (15 g.) were dissolved in liquid ammonia (130 c.c.) in a Dewar flask (350 c.c.), and sodium (7 g.) added in small pieces with good stirring as rapidly as possible without the reaction becoming uncontrollable (about 45 minutes). When the blue colour had disappeared, the pasty mass was decomposed by cautious addition of water (100 c.c.), and the oil collected with ether. With the methoxy-compounds this product, consisting chiefly of the dihydro-derivative, could be distilled; with the amines some decomposition occurred in presence of water, but the dihydro-derivative could be isolated if necessary by direct extraction of the reaction mixture with dry ether. Hydrolysis to the acid-stable form of the ketone was accomplished by refluxing the dihydro-derivative with a mixture of concentrated sulphuric acid (6 c.c.) and water (25 c.c.) for 25 minutes, followed by saturation with ammonium sulphate and extraction with ether. Hydrolysis of the methoxyalkyldihydrobenzenes to the $\beta\gamma$-unsaturated ketones was carried out by shaking with a saturated aqueous solution of sodium hydrogen sulphite (10 g.) for 12 hours. The solid derivative was filtered off, and decomposed by addition to a solution of sodium carbonate (5 g.) in water (15 c.c.), and the ketone extracted with ether and distilled under reduced pressure. The $\beta\gamma$-unsaturated 2 : 4-dinitrophenylhydrazones were prepared by adding the dihydro-derivative or the $\beta\gamma$-unsaturated ketone to excess of 2 : 4-dinitrophenylhydrazine in cold alcoholic sulphuric acid (5%), the derivative being filtered off and washed with aqueous sodium carbonate and then water to remove any acid which might isomerise it on recrystallisation. They were converted into the $\alpha\beta$-unsaturated derivatives by refluxing for 3 minutes with a drop of sulphuric acid in alcohol, with addition of benzene in the case of the less soluble ones. The $\beta\gamma$-unsaturated semicarbazones were obtained in the usual manner from the ketones, or from the dihydro-amines by shaking with aqueous semicarbazide hydrochloride until they dissolved, and then adding sodium acetate.

Method B.—The dihydro-derivatives were obtained by method A, and further treated with a solution of sodium (7 g.) in ammonia (150 c.c.) for 6—8 hours. In some cases the dihydro-derivatives were not isolated from the initial reduction, the extra sodium being added directly. Control experiments showed that identical results were obtained by either method. The products were worked up and hydrolysed as under method A, the ketonic fraction alone being examined, except with the tolyl methyl ethers where the product was distilled before hydrolysis, and the lower-boiling hydrocarbon fraction separated.

Method C.—Calcium (15 g.) was dissolved in ammonia (100 c.c.) in small portions, most of the ammonia evaporated until the golden metallic oil was on the point of solidification, and dry ether (75 c.c.) added with vigorous swirling to obtain the calcium hexammine as a golden sand. To this was added the compound (20 g.) in ether (75 c.c.), and the mixture left for 36—72 hours according to the rate of reaction. It was then very cautiously added to crushed ice under nitrogen, and the product extracted with ether by the aid of a centrifuge. After drying and removal of the solvent, the oil was refluxed for 30 minutes with a mixture of concentrated sulphuric acid (10 c.c.) and water (35 c.c.). The ketones (from the amines) or their derivatives (from the methoxy-compounds) were isolated as under method A.

Dimethylaniline.—Method A gave Δ^3-*cyclo*hexenone (3·2 g.), b. p. 163—167° (Found: C, 74·5; H, 8·7. Calc. for C_6H_8O: C, 75·0; H, 8·3%), $\lambda_{max.}$ 2245 A.; $\epsilon_{max.}$ 8440; 2 : 4-dinitrophenylhydrazone, m. p. 165—166°, undepressed by an authentic specimen; semicarbazone (from water), m. p. 161—162° (Found: C, 54·6; H, 7·5. Calc. for $C_7H_{11}ON_3$: C, 54·8; H, 7·2%); $\lambda_{max.}$ 2627 A.; $\epsilon_{max.}$ 16,460. Kötz and Grethe (*J. pr. Chem.*, 1909, **80**, 499) give m. p. 161° for Δ^3-*cyclo*hexenone semicarbazone. Δ^3-cyclo*Hexenone* 2 : 4-*dinitrophenylhydrazone* formed orange-yellow plates from alcohol, m. p. 131—132°; $\lambda_{max.}$ 3690 A.; $\epsilon_{max.}$ 18,700 (Found: C, 52·5; H, 4·4. $C_{12}H_{12}O_4N_4$ requires C, 52·2; H, 4·3%). Treatment with acid converted it into the above derivative, m. p. 165—166°. Δ^3-cyclo*Hexenone semicarbazone* formed colourless needles from water, m. p. 146—147°, $\lambda_{max.}$ 2288 A.; $\epsilon_{max.}$ 12,350 (Found: C, 54·5; H, 7·2. $C_7H_{11}ON_3$ requires C, 54·8; H, 7·2%).

Method B gave *cyclo*hexanone (2·9 g.), b. p. 150—152° (Found: C, 73·1; H, 10·4. Calc. for $C_6H_{10}O$: C, 73·5; H, 10·2%); 2 : 4-dinitrophenylhydrazone, orange-yellow plates, m. p. 155—156°, undepressed by an authentic specimen, m. p. 157—158°.

Method C gave in small yield *cyclo*hexanone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 157—158°.

Anisole.—Dihydroanisole (method A) gave Δ^3-*cyclo*hexenone 2 : 4-dinitrophenylhydrazone, m. p. 132—133°, undepressed by a specimen obtained as above. Methods B and C gave *cyclo*hexanone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 157—158°.

Dimethyl-o-toluidine.—Method A gave the *dihydro*-derivative containing a little starting material, b. p. 75—78°/14 mm. (Found: C, 79·2; H, 10·6. $C_9H_{13}N$ requires C, 78·9; H, 10·9%). The ketone obtained on hydrolysis (3·25 g.) had b. p. 60—75°/15 mm., $\lambda_{max.}$ 2263 A.; $\epsilon_{max.}$ 4490 (Found: C, 75·9; H, 9·3. Calc. for $C_7H_{10}O$: C, 76·35; H, 9·1%). The position of the absorption maximum corresponds to a β-alkyl $\alpha\beta$-unsaturated ketone (Woodward, *J. Amer. Chem. Soc.*, 1942, **64**, 716) and the major constituent is therefore probably 6-methyl-Δ^2-*cyclo*hexenone. Redistillation gave two fractions, b. p. 164—167° (2·6 g.), and b. p. 167—174° (0·2 g.). The former gave a semicarbazone, m. p. 172°, and the latter a semicarbazone, m. p. 198—200°. Since Kötz and Steinhorst (*Annalen*, 1911, **379**, 17) give m. p. 177—178° for 6-methyl-Δ^2-*cyclo*hexenone semicarbazone, and Wallach (*Annalen*, 1908, **369**, 303) gives m. p. 207—208° for 2-methyl-Δ^2-*cyclo*hexenone semicarbazone the above are probably these compounds in a slightly impure form. On treatment

with alcoholic 2 : 4-dinitrophenylhydrazine sulphate they gave 2 : 4-*dinitrophenylhydrazones* respectively as orange-red elongated prisms, m. p. 156—157° (Found: C, 53·8; H, 4·6. $C_{13}H_{14}O_4N_4$ requires C, 53·8; H, 4·8%), and as dark red plates, m. p. 198—199°, undepressed by the derivative of 2-methyl-Δ^2-*cyclo*hexenone, m. p. 203° (Found: C, 54·2; H, 4·8. $C_{13}H_{14}O_4N_4$ requires C, 53·8; H, 4·8%). The latter derivatives were obtained directly from the crude ketone by crystallising the 2 : 4-dinitrophenylhydrazone repeatedly from benzene–alcohol, the second being less soluble and present in smaller amount. Treatment of the ketone with excess of 2 : 4-dinitrophenylhydrazine sulphate in hot alcohol gave an orange, rather insoluble substance; recrystallised from pyridine, this had m. p. 176—177° (Found: C, 46·8; H, 4·1. $C_{19}H_{20}O_8N_8$ requires C, 46·7; H, 4·1%). Since it could not be obtained from 2-methyl-Δ^2-*cyclo*hexenone it is probably 6-*methyl*-Δ^2-cyclo*hexenone* 2 : 4-*dinitrophenylhydrazino*-2 : 4-*dinitrophenylhydrazone*.

Method B produced a ketone (0·5 g.), b. p. 160—180°, which gave rise to a little of the last substance, m. p. 176—177°, but chiefly 2-methyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone, m. p. 131—132°, undepressed by an authentic specimen, m. p. 134—135°.

Method C gave a ketone (3·2 g.), b. p. 60—66°/18 mm., which was separated into two fractions: b. p. 162—164° (2·3 g.) and b. p. 166—169° (0·4 g.). The former was chiefly 2-methyl*cyclo*hexanone (Found: C, 75·0; H, 10·7. Calc. for $C_7H_{12}O$: C, 75·0; H, 10·7%), and gave the 2 : 4-dinitrophenylhydrazone as orange plates, m. p. 132—133°, after several crystallisations from alcohol, undepressed by an authentic specimen, m. p. 134—135°. The absorption ($\lambda_{max.}$ 2263 A.; $\epsilon_{max.}$ 2085) indicated the presence of some of the *cyclo*hexenone. The second fraction contained more of this ($\lambda_{max.}$ 2263 A.; $\epsilon_{max.}$ 3810) and gave a red 2 : 4-dinitrophenylhydrazone, m. p. 135—139°, undepressed by the derivative above, m. p. 156—157°, but depressed by that of 2-methyl*cyclo*hexanone, m. p. 134—135°.

o-*Tolyl Methyl Ether*.—The product obtained by method A contained about 45% of dihydro-derivative, since 1·0 g., treated with 2 : 4-dinitrophenylhydrazine (2·0 g.) in 5% alcoholic sulphuric acid in the cold, gave a 2 : 4-*dinitrophenylhydrazone* as orange prisms, m. p. 135—137° (1·0 g.) (Found: C, 53·8; H, 4·6. $C_{13}H_{14}O_4N_4$ requires C, 53·8; H, 4·8%). The ketone obtained after acid hydrolysis must consist of the same mixture of substances as in the case of dimethyl-*o*-toluidine since it gave the two 2 : 4-dinitrophenylhydrazones, m. p. 155—156° and m. p. 198—199°.

Method B gave the 2 : 4-dinitrophenylhydrazone of 2-methyl*cyclo*hexanone, m. p. 133—134°, in small yield. In addition, a small amount of hydrocarbon, b. p. 105—110°, was obtained, which gave methyl-Δ^1-*cyclo*hexene nitrolpiperidine, m. p. 146—147°, undepressed by an authentic specimen, m. p. 146—147°.

Method C gave a mixed 2 : 4-dinitrophenylhydrazone from which a little of the 2-methyl-Δ^2-*cyclo*hexenone derivative, m. p. 199—200°, was obtained. The main bulk formed orange-red, elongated prisms from benzene–alcohol, m. p. 130—136°, which appeared to consist mainly of the 6-methyl-Δ^2-*cyclo*hexenone derivative, since on refluxing with 2 : 4-dinitrophenylhydrazine in alcoholic sulphuric acid it gave the insoluble 2 : 4-dinitrophenylhydrazino-2 : 4-dinitrophenylhydrazone, m. p. 175—176°.

Dimethyl-m-*toluidine*.—Method A gave 3-methyl-Δ^2-*cyclo*hexenone as a colourless oil (3·1 g.), b. p. 190—195° (Found: C, 75·8; H, 9·1. Calc. for $C_7H_{10}O$: C, 76·35; H, 9·1%); $\lambda_{max.}$ 2320 A.; $\epsilon_{max.}$ 11,290; Evans and Gillam (*J.*, 1941, 815) give $\lambda_{max.}$ 2350 A.; $\epsilon_{max.}$ 12,930. The 2 : 4-dinitrophenylhydrazone formed dark red plates from benzene–alcohol, m. p. 173—174°, and the semicarbazone colourless prisms from alcohol, m. p. 200—201°, $\lambda_{max.}$ 2640 A.; $\epsilon_{max.}$ 24,500. Treatment of the crude dihydro-derivative with semicarbazide hydrochloride followed by sodium acetate gave 3-*methyl*-Δ^2-cyclo*hexenone semicarbazone* as colourless plates from alcohol, m. p. 158—159°; $\lambda_{max.}$ 2283 A.; $\epsilon_{max.}$ 11,410 (Found: C, 57·3; H, 7·8. $C_9H_{15}ON_3$ requires C, 57·5; H, 7·8%). It was isomerised by refluxing with 5% aqueous-alcoholic semicarbazide hydrochloride for 30 minutes to the above $\alpha\beta$-unsaturated semicarbazone, m. p. 200—201°.

Method B gave a product which still gave rise to the 2 : 4-dinitrophenylhydrazone of 3-methyl-Δ^2-*cyclo*hexenone, m. p. 173—174°, but on addition of further sodium (5 g.) and ammonia (100 c.c.) and standing for 12 hours, the product then gave a very small yield of 3-methyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone as orange elongated prisms from benzene–alcohol, m. p. 156—157° (Found: C, 53·3; H, 5·4. Calc. for $C_{13}H_{16}O_4N_4$: C, 53·4; H, 5·5%). Allen and Richmond (*J. Org. Chem.*, 1937, **2**, 226) give m. p. 155°. The semicarbazone formed colourless prisms from alcohol, m. p. 181—182°.

Method C gave the ketonic hydrolysis product as an oil, b. p. 185—195° (0·8 g.), which gave the 2 : 4-dinitrophenylhydrazone, m. p. 173—174°, and semicarbazido-semicarbazone, m. p. 214°, of 3-methyl-Δ^2-*cyclo*hexenone.

m-*Tolyl Methyl Ether*.—Method A gave the dihydro-derivative as a colourless oil, b. p. 168—170° (cf. Part I). This substance (1·00 g.) gave with a hot solution of 2 : 4-dinitrophenylhydrazine (2·0 g.) in alcoholic sulphuric acid the 2 : 4-dinitrophenylhydrazone (2·0 g.) of 3-methyl-Δ^2-*cyclo*hexenone, m. p. 173—174° (2·15 g.), corresponding to a 94% content of dihydro-derivative. Hydrolysis of the latter (5 g.) with a saturated solution of sodium hydrogen sulphite (10 g.) gave a solid bisulphite compound (4 g.), which was decomposed with a solution of sodium carbonate (5 g.) in water (12 c.c.). Extraction with ether gave 3-*methyl*-Δ^2-cyclo*hexenone* as a colourless oil with a marked odour, b. p. 70°/18 mm. (Found: C, 76·1; H, 9·3. $C_7H_{10}O$ requires C, 76·35; H, 9·1%). From the presence of absorption at $\lambda_{max.}$ 2330 A.; $\epsilon_{max.}$ 2050, it appears to contain some 16% of the isomeric 3-methyl-Δ^2-*cyclo*hexenone, into which it is very readily converted by the action of acids. The *R* band at $\lambda_{max.}$ 2800 A.; $\epsilon_{max.}$ 19, is at a considerably shorter wave-length than the value $\lambda_{max.}$ 3100 A.; $\epsilon_{max.}$ 48 given for the latter ketone by Evans and Gillam (*loc. cit.*). It gave the semicarbazone as colourless plates, m. p. 159—160°.

Method B gave two fractions: b. p. 105—111° (2·2 g.) and b. p. 160—165° (0·6 g.). The former was a methyl*cyclo*hexene, $n_D^{16°}$ 1·4526 (Found: C, 87·2; H, 12·8. Calc. for C_7H_{12}: C, 87·5; H, 12·5%). It contained methyl-Δ^1-*cyclo*hexene, since it gave a solid nitrosochloride from which was obtained the nitrolpiperidine, m. p. 147—148°, undepressed by an authentic specimen (Found: C, 68·6; H, 10·4. Calc. for $C_{13}H_{22}ON_2$: C, 68·6; H, 10·5%). Treatment of the second fraction with 2 : 4-dinitrophenylhydrazine gave a mixed product, but after further treatment with sodium in ammonia it gave a small yield of 3-methyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone, m. p. 156—157° (Found: C, 53·3; H, 5·4. Calc. for $C_{13}H_{16}O_4N_4$: C, 53·4; H, 5·4%).

Method C, but with omission of the ether ordinarily used as a solvent, gave two fractions: b. p. 100—110° (0·8 g.) and b. p. 167—175° (16 g.). The former gave the nitrolpiperidine of methyl-Δ^1-*cyclo*hexene, m. p. 145—146°, the latter a small yield of 3-methyl-Δ^2-*cyclo*hexenone 2 : 4-dinitrophenylhydrazone, m. p. 173—174°.

Dimethyl-p-*toluidine*.—Method A gave 4-methyl-Δ^3-*cyclo*hexenone (4·1 g.), b. p. 74°/17 mm. or 169—172°/755 mm. (Found: C, 75·9; H, 9·6. Calc. for $C_7H_{10}O$: C, 76·35; H, 9·1%). The absence of a maximum at 2260 A. ($\epsilon_{mol.}$ 870) confirmed its formulation as the $\beta\gamma$-unsaturated ketone. It was also obtained readily by the bisulphite method. The 2 : 4-*dinitrophenylhydrazone* formed orange prisms, m. p. 120—121°, $\lambda_{max.}$ 3680 A.; $\epsilon_{max.}$ 20,200 (Found: C, 53·8; H, 4·8. $C_{13}H_{14}O_4N_4$ requires C, 53·8; H, 4·8%). This was converted by refluxing with alcoholic sulphuric acid for a minute into 4-*methyl*-Δ^2-cyclo*hexenone* 2 : 4-*dinitrophenylhydrazone*, dark red prisms from benzene–alcohol, m. p. 173—174°, $\lambda_{max.}$ 3830 A.; $\epsilon_{max.}$ 22,150 (Found: C, 53·8; H, 4·7. $C_{13}H_{14}O_4N_4$ requires C, 53·8; H, 4·8%). The absorption of 4-methyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone ($\lambda_{max.}$ 3685 A.; $\epsilon_{max.}$ 19,100) was almost identical with that of the former derivative. 4-Methyl-Δ^3-*cyclo*hexenone semicarbazone formed colourless prisms, m. p. 188—189°, $\lambda_{max.}$ 2330 A.; $\epsilon_{max.}$ 11,300.

After the ketone (3 g.) had been refluxed with 3% aqueous sulphuric acid for 6 hours it was redistilled: (i), b. p.

170—173°; (ii), b. p. 173—178°. The former gave the same derivatives as the starting material; the latter ($\lambda_{max.}$ 2280 A.; $\epsilon_{max.}$ 6780) contained some 4-methyl-Δ^3-*cyclo*hexenone, and gave in the cold a mixture of the 2 : 4-dinitrophenylhydrazones, m. p. 120—121° and 173—174°, the latter being separated by its lower solubility in alcohol. It appears, therefore, that the $\beta\gamma$-unsaturated ketone is only isomerised to a small extent by acid.

Method B gave a ketone (1·3 g.), b. p. 165—172°, from which the 2 : 4-dinitrophenylhydrazone of 4-methyl*cyclo*hexanone, m. p. and mixed m. p. 133—134°, could be obtained (Found : C, 53·0; H, 5·5. Calc. for $C_{13}H_{16}O_4N_4$: C, 53·4; H, 5·5%). The semicarbazone crystallised as prisms from alcohol, m. p. and mixed m. p. 196° (Found : C, 56·8; H, 8·9. Calc. for $C_8H_{15}ON_3$: C, 56·8; H, 8·9%).

Method C also gave a small yield of 4-methyl*cyclo*hexanone, identified by the above derivatives, m. p. 133—134° and 196°.

p-*Tolyl Methyl Ether*.—Method A gave the dihydro-derivative (5 g.), b. p. 167—170°, shown by the action of 2 : 4-dinitrophenylhydrazine sulphate to be 94% pure (cf. *m*-tolyl methyl ether). The 2 : 4-dinitrophenylhydrazone, m. p. 120—121°, was identical with that obtained from dimethyl-*p*-toluidine.

Further reduction of the dihydro-derivative by method B gave (i), b. p. 105—110° (0·7 g.), and (ii), b. p. 155—165° (0·3 g.). The former gave the nitrolpiperidine of methyl-Δ^1-*cyclo*hexene, m. p. 146—147°, and the latter the 2 : 4-dinitrophenylhydrazone of 4-methyl*cyclo*hexanone, m. p. 132—133°. This derivative was also obtained from the product of reduction by method C.

Dimethyl-p-*cumidine*.—Method A gave a ketonic product (3·5 g.), b. p. 97—98°/16 mm. It gave in the cold 4-iso*propyl*-Δ^3-cyclo*hexenone* 2 : 4-*dinitrophenylhydrazone* as golden plates (from alcohol), m. p. 107—108° (Found : C, 56·3; H, 5·5. $C_{15}H_{18}O_4N_4$ requires C, 56·6; H, 5·7%). On refluxing with dilute alcoholic sulphuric acid this gave the derivative of 4-*iso*propyl-Δ^3-*cyclo*hexenone as orange-red elongated prisms from benzene–alcohol, m. p. 135—136° (Found : C, 56·6; H, 5·8. Calc. for $C_{15}H_{18}O_4N_4$: C, 56·6; H, 5·7%). Berry, Macbeth, and Swanson (*J.*, 1937, 987) give m. p. 138° for the derivative obtained from the optically active ketone.

2 : 4-*Dimethylanisole*.—Method A gave rise to a 2 : 4-dinitrophenylhydrazone, prepared in hot solution, as orange-red prisms, m. p. 164—165° (Found : C, 55·2; H, 5·2. $C_{14}H_{16}O_4N_4$ requires C, 55·2; H, 5·3%). Since the product from method B gave the same derivative, no further reduction had taken place. Method C proceeded very slowly, and after 14 days the small amount of neutral material gave the above derivative, m. p. 164—165°. The chief product (70% yield) was *m*-4-xylenol, identified as 2 : 4-dimethylphenoxyacetic acid, m. p. and mixed m. p. 138—139°.

6-*Methoxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—The dihydro-derivative prepared by method A was hydrolysed with sodium hydrogen sulphite, and the solid adduct steam-distilled from 10% aqueous sodium carbonate. The 2-*keto*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydronaphthalene* so obtained was a colourless oil with a marked odour, b. p. 117°/12 mm. (Found : C, 79·6; H, 9·2. $C_{10}H_{14}O$ requires C, 80·0; H, 9·3%). The 2 : 4-*dinitrophenylhydrazone*, also obtained directly in the cold from the dihydro-compound, formed orange-red elongated plates from benzene–alcohol, m. p. 176—177° (Found : C, 58·3; H, 5·4. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·45%). On being refluxed with alcoholic sulphuric acid for a minute this was converted into 2-*keto*-2 : 3 : 4 : 5 : 6 : 7 : 8 : 10-*octahydronaphthalene* 2 : 4-*dinitrophenylhydrazone*, which formed dark red plates from benzene–alcohol, m. p. 171—172° (Found : C, 58·2; H, 5·4. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·45%).

2 : 5-*Dihydro*-m-*xylene*.—Prepared as in Part I, the hydrocarbon, b. p. 141—142°, contained 8% of *m*-xylene as estimated by the intensity of its ultra-violet absorption bands. Hydrocarbon (12 g.) in ether (40 c.c.) was left with calcium hexammine (from calcium, 10 g.) for 36 hours. The greyish mass was then added carefully to crushed ice under nitrogen, slightly acidified with dilute hydrochloric acid, and the oil distilled. The product (6·8 g.) was a dimethyl*cyclo*hexene, b. p. 124—129°, $n_D^{18°}$ 1·4530 (Found : C, 87·4; H, 12·5. Calc. for C_8H_{14} : C, 87·3; H, 12·7%). Treatment with amyl nitrite and hydrogen chloride at − 15° gave no solid nitrosochloride, but addition of petrol to the blue oil gave a white solid. A portion of this was crystallised from benzene, forming colourless prisms, m. p. 137—138°. The bulk was converted into a mixture of nitrolpiperidines, the principal constituent of which was obtained as colourless prisms, m. p. 157—158°, by several crystallisations from alcohol (Found : C, 69·4; H, 10·7. $C_{13}H_{24}ON_2$ requires C, 69·6; H, 10·7%). Since two stereoisomers are possible the production of a mixture is not unexpected.

m-*Xylene*.—Carried out as above, the reduction gave a product still containing a considerable amount of *m*-xylene, and was repeated. The product was a colourless oil, b. p. 124—129°, $n_D^{20°}$ 1·4530 (Found : C, 87·6; H, 12·4. Calc. for C_8H_{14} : C, 87·3; H, 12·7%). The intensity of its ultra-violet absorption bands indicated the presence of about 8% of *m*-xylene; the analytical figures calculated for this mixture are : C, 87·6; H, 12·4%. The nitrosochloride, obtained as above, had m. p. 123—126° (crude), m. p. 137—138° after recrystallisation from benzene. Kazanskii (*loc. cit.*) gives m. p. 117—118° for this nitrosochloride. It gave a nitrolpiperidine, m. p. 157—158°, undepressed by the derivative obtained above.

p-*Bromoanisole and* o-*Chloroanisole*.—Reduction was by method C, and the reaction was controlled by ice-cooling. The product was separated into two fractions : (i), b. p. 150—160° (5 g.), and (ii), b. p. 160—170° (1·1 g.). The former was shown by demethylation with hydrobromic acid to consist chiefly of anisole; the latter gave the 2 : 4-dinitrophenylhydrazone of Δ^3-*cyclo*hexenone, m. p. and mixed m. p. 132—133°, converted by acid into the derivative of Δ^3-*cyclo*hexenone, m. p. 165—166°. 4-Chloro-2-methoxytoluene gave a quantitative yield of *o*-tolyl methyl ether, identified by demethylation and conversion into 2-methylphenoxyacetic acid, m. p. 150°.

The ultra-violet absorption measurements were carried out by Dr. F. B. Strauss, in ethyl alcoholic solution, except with the 2 : 4-dinitrophenylhydrazones which were dissolved in chloroform.

The author wishes to express his gratitude to Imperial Chemical Industries Ltd., Dyestuffs Division, for financial assistance.

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120. *The Preparation and Bacteriostatic Properties of some Amines derived from Citral.*

By A. G. Caldwell and E. R. H. Jones.

Aldimines obtained by condensation of citral with primary and secondary amines are hydrogenated to saturated secondary and tertiary amines using Raney nickel catalyst at 120° under about 140 atmospheres' pressure. The light absorption properties of the unsaturated aldimines, which are similar to those of the parent aldehyde, are discussed.

HYDROGENATION of citraloxime with Raney nickel catalyst in the presence of ammonia gives a 60% yield of tetrahydrogeranylamine (*hydrochloride*, m. p. 104—105°) and 30% of di(tetrahydrogeranyl)amine.

Aldimines from citral and *n*-butylamine and *cyclo*hexylamine have been prepared by a method similar to that of Campbell, Sommers, and Campbell (*J. Amer. Chem. Soc.*, 1944, **66**, 82) and it has been found that the hydrogenation of these aldimines with a Raney nickel catalyst at about 120° under pressures of 140 atmospheres proceeds readily and gives excellent yields of the saturated secondary amines (cf. Henze and Humphreys, *ibid.*, 1942, **64**, 2878).

The hydrogenation of the aldimine derived from *cyclo*hexylamine proceeds in two distinct stages. Under moderate conditions of temperature and pressure in *cyclo*hexane solution, cyclo*hexylcitronellylamine* (I) can be obtained in about 70% yield. It gives acetone (80% yield) on ozonolysis and, on hydrogenation under

$$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}NH{\cdot}C_6H_{11} \quad (I.)$$

rather more vigorous conditions, yields the same saturated secondary amine as does the original aldimine when similarly treated. This resistance to hydrogenation of the terminal double bond in compounds of the citral series has been encountered by earlier workers (Skita, *Ber.*, 1909, **42**, 1634; Armstrong and Hilditch, *Proc. Roy. Soc.*, 1925, *A*, **108**, 121).

Owing to the presence of the C=C—C=N system, both of the aldimines mentioned above absorb intensely in the ultra-violet in the region of 2400 A. The aldimines, like the oximes (Evans and Gillam, *J.*, 1943, 565), therefore exhibit much the same light absorption properties as the parent carbonyl compounds and, generally speaking, the chromophores C=C—C=C, C=C—C=O and C=C—C=N, appear to be very similar in their properties in so far as high-intensity absorption is concerned. The considerable bathochromic effects observed with the semicarbazones and thiosemicarbazones (Evans and Gillam, *loc. cit.*) cannot therefore be attributed, as considered by these authors, to the C=C—C=N chromophore, and the suggestion that C=C—C=N—NH chromophores are involved does not explain the difference between the semicarbazones and their thio-analogues. As has already been suggested (Braude and Jones, *J.*, 1945, 498) these effects must be connected with the marked bathochromic effects and conjugating power of nitrogen (Bowden, Braude, Jones, and Weedon, this vol., p. 45) and (in the thiosemicarbazones) sulphur atoms (unpublished observations), and extended chromophores such as C=C—C=N—NH—C=O and C=C—C=N—NH—C=S are probably involved in these cases. The similarity between the light absorption of the oximes and the aldimines is explained both by the absence of any chromophoric group attached to the second oxygen valency and by the almost negligible bathochromic effect and conjugating power of the oxygen atom.

Mannich, Handke, and Roth (*Ber.*, 1936, **69**, 2112) examined the condensation of αβ-unsaturated aldehydes with primary amines and found that ethylenic diamines [*e.g.*, $CHMe(NMe_2){\cdot}CH{:}CH{\cdot}NMe_2$] were initially formed. On heating, these eliminated a molecule of secondary amine giving aminobutadienes (Langenbeck, Gödde, Weschky, and Schaller, *Ber.*, 1942, **75**, 232; cf. Bowden, Braude, Jones, and Weedon, *loc. cit.*). It was observed by the original authors that the intermediate diamines cannot be isolated from condensations with the higher aldehydes, and we have found that condensation of citral with di-*n*-butylamine gives the triply unsaturated tertiary *amine* (II), hydrogenated to the saturated *amine* with a Raney nickel catalyst. The light absorption

$$CMe_2{:}CH{\cdot}CH_2{\cdot}CH{:}CMe{\cdot}CH{:}CH{\cdot}NBu_2 \quad (II.)$$

properties of this compound (maxima at 2820 and 2920 A.) are fully in accordance with expectations, in view of the bathochromic and hyperchromic effects already observed (Bowden, Braude, Jones, and Weedon, *loc. cit.*) when nitrogen atoms are attached to the terminal carbon atoms of olefinic or polyene systems.

Bacteriostasis tests, against a variety of bacteria, on the hydrochlorides of the saturated amines described above, and also on the hydrochloride of the ethylenic amine (I), were kindly carried by Dr. A. T. Fuller of the National Institute for Medical Research, through the courtesy of the Director, Dr. C. R. Harington, F.R.S. The activities observed are roughly of the same order as those already reported for the straight chain amines (Fuller, *Biochem. J.*, 1942, **36**, 548) and, as was found with the latter, they are considerably diminished in serum-broth media.

EXPERIMENTAL.

Light absorption data obtained using alcoholic solutions.

Hydrogenation of Citraloxime with Raney Nickel Catalyst.—(Cf. Skita and Keil, *Ber.*, 1928, **61**, 1452, who employed colloidal platinum.) The oxime (20 g.), dissolved in alcohol (180 c.c.) containing ammonia (*d* 0·88; 15 c.c.), was hydrogenated at 100°/140 atm. for 12 hours using Raney nickel (4—5 g.). The product consisted of (*a*) tetrahydrogeranylamine (10·5 g.), b. p. 60—61°/5 mm., $n_D^{16°}$ 1·4382 (Wallach and Behnke, *Annalen*, 1912, **389**, 197, give b. p. 202—203°, $n_D^{21°}$ 1·4316), giving a *hydrochloride* which crystallised from acetone–light petroleum (b. p. 40—60°) in plates, m. p. 104—105° (Found: N, 7·4. $C_{10}H_{24}NCl$ requires N, 7·25%), and (*b*) di(tetrahydrogeranyl)amine (5·3 g.), b. p. 140°/5 mm., $n_D^{16°}$ 1·4516, hydrochloride, m. p. 140—141° (Skita and Keil, *loc. cit.*, give b. p. 192—193°/15 mm., hydrochloride, m. p. 141—142°).

n-*Butyltetrahydrogeranylamine* (n-*butyl*-3 : 7-*dimethyloctylamine*).—*n*-Butylamine (24·5 g.) was stirred at 0°, and citral (51·5 g.) was added during 2 hours. After stirring for a further hour the product was isolated with ether, the ethereal solution being dried (powdered KOH) at 0° for 20 hours. Evaporation and distillation from a little potassium hydroxide gave the *aldimine* (51·7 g.), b. p. 97—98°/4 mm., $n_D^{18°}$ 1·4879, as a colourless liquid which darkened rapidly in air (Found: C, 81·15; H, 12·05. $C_{14}H_{31}N$ requires C, 81·1; H, 12·15%). Light absorption: Maximum, 2400 A., log ε = 4·35.

The aldimine (20 g.), dissolved in methyl alcohol (180 c.c.), was hydrogenated at 120°/140 atm. for 9 hours using Raney nickel (4—5 g.), giving n-*butyltetrahydrogeranylamine* (17·1 g.), b. p. 90—92°/4 mm., $n_D^{20°}$ 1·4384 (Found: C, 78·9; H, 14·4. $C_{14}H_{31}N$ requires C, 78·8; H, 14·65%). The *hydrochloride*, prepared with dry hydrogen chloride in ether

and crystallised from acetone and from ethyl acetate, had m. p. 196—197° (Found: N, 5·65. $C_{14}H_{32}NCl$ requires N, 5·6%).

cyclo*Hexyltetrahydrogeranylamine* (cyclo*hexyl*-3 : 7-*dimethyloctylamine*).—(Cf. Skita and Keil, *loc. cit.*) The aldimine, prepared in 70% yield by the method described above, had b. p. 125°/4 mm., $n_D^{18°}$ 1·5101 (Found: C, 82·55; H, 11·45. Calc. for $C_{16}H_{33}N$: C, 82·35; H, 11·65%). Light absorption: Maxima, 2390 and 2490 A.; log ε = 4·34 in each case. Reduction of the aldimine (15 g.) in methyl alcohol (150 c.c.) with hydrogen at 120°/140 atm. for 7 hours using Raney nickel (4—5 g.) gave the saturated amine (11·3 g.) with b. p. 103°/4 mm., $n_D^{20°}$ 1·4612 (Found: C, 80·25; H, 13·6. Calc. for $C_{16}H_{33}N$: C, 80·25; H, 13·9%). The hydrochloride had m. p. 153—153·5° (Skita and Keil, *loc. cit.*, give m. p. 154—155°) (Found: N, 5·05. Calc. for $C_{16}H_{34}NCl$: N, 5·1%).

cyclo*Hexylcitronellylamine* (cyclo*hexyl*-3 : 7-*dimethyloct*-6-*enylamine*).—The crude but dried aldimine from *cyclo*hexylamine (26 g.) and citral (40 g.) was dissolved in *cyclo*hexane (85 c.c.) and hydrogenated at 100°/90 atm. for 10 hours in the presence of Raney nickel (4—5 g.). The agitation of the reaction mixture in this case was probably less efficient than in the hydrogenation described immediately above. Isolation in the normal manner gave cyclo*hexylcitronellylamine* (43·2 g.), b. p. 112—113°/4 mm., $n_D^{16°}$ 1·4780 (Found: C, 80·95; H, 12·85. $C_{16}H_{31}N$ requires C, 80·95; H, 13·15%). The *hydrochloride* crystallised from acetone–light petroleum (b. p. 40—60°) in micro-crystals, m. p. 125—126° (Found: N, 5·15. $C_{16}H_{32}NCl$ requires N, 5·15%).

Ozonolysis of cyclo*Hexylcitronellylamine*.—The amine (2 g.) was dissolved in AnalaR acetic acid (35 c.c.), and ozonised oxygen was passed into the solution until absorption ceased (*ca.* 4 hours). Water (150 c.c.) was added and the solution was distilled in steam. The first 30 c.c. of distillate yielded 1·6 g. (80% of theory) of acetone 2 : 4-dinitrophenylhydrazone, m. p. 123—124° undepressed on admixture with an authentic specimen, on treatment with 2 : 4-dinitrophenylhydrazine sulphate solution.

Hydrogenation of cyclo*Hexylcitronellylamine*.—A solution of the amine (25 g.) in methyl alcohol (200 c.c.) was hydrogenated at 100°/140 atm. for 9 hours using Raney nickel (4—5 g.) giving the saturated amine described above, b. p. 110—112°/5 mm., $n_D^{22°}$ 1·4597; the hydrochloride had m. p. 152·5—153°, undepressed on admixture with an authentic specimen.

Di-n-*butyl*-3 : 7-*dimethylocta*-1 : 3 : 6-*trienylamine*.—Citral (38 g.) was added during 25 minutes to stirred di-*n*-butylamine (49 g.) at 0° and stirring was continued for a further 1½ hours. The mixture was treated with anhydrous potassium carbonate and the product isolated with ether, the ethereal solution being dried at 0° for 16 hours (K_2CO_3). Distillation gave the tertiary *amine* (40·5 g.), as a pale yellow mobile oil, b. p. 144—145°/4 mm., $n_D^{20°}$ 1·5129 (Found: C, 82·45; H, 12·85. $C_{16}H_{29}N$ requires C, 82·05; H, 12·6%). Light absorption: Maxima, 2820 and 2920 A.; log ε = 4·37 in each case.

Di-n-*butyltetrahydrogeranylamine* (*di*-n-*butyl*-3 : 7-*dimethyloctylamine*).—The above unsaturated amine (20 g.), on hydrogenation in methyl alcohol (180 c.c.) at 120°/140 atm. with Raney nickel (5—6 g.) for 14 hours, gave the saturated tertiary *amine* (13·9 g.), b. p. 116—117°/4 mm., $n_D^{18°}$ 1·4431 (Found: C, 80·35; H, 14·6. $C_{16}H_{35}N$ requires C, 80·25; H, 14·6%).

The authors thank Dr. E. A. Braude for the light absorption data and the Colonial Products Research Council, under whose auspices this work was carried out.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, S.W.7. [*Received, November 29th*, 1945.]

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121. *Rearrangements of Aldoximes into Amides with Raney Nickel. Stereoisomeric Geranamides.*

By A. G. CALDWELL and E. R. H. JONES.

When the oximes of tetrahydrocitral, citronellal, and citral are heated with Raney nickel, the corresponding amides are obtained in yields of 70, 50, and 40% respectively. From citraloxime, two crystalline *geranamides* are formed and these are readily separated by chromatography. Since they both yield *a-cyclo*geranamide (III) on boiling with dilute acid and both give high yields of acetone on ozonolysis, they are formulated as geometrical isomerides of the *iso*propylidene structure (I).

WHILE studying the hydrogenation of aldoximes using a Raney nickel catalyst, Paul (*Bull. Soc. chim.*, 1937, **4**, 1116) noted the formation of small amounts of the amides of the corresponding acids. Further investigation established that the oximes of saturated aldehydes are practically quantitatively isomerised into amides on heating

$$R{\cdot}CH{:}NOH \longrightarrow R{\cdot}CO{\cdot}NH_2$$

with Raney nickel at about 100°. Bryson and Dwyer (*J. Proc. Roy. Soc., New South Wales*, 1941, **74**, 471) have provided evidence for Paul's suggestion that the reaction proceeds *via* an aldoxime–nickel complex, the rearrangement of which is promoted by traces of iron or aluminium.

Under Paul's conditions the oximes of tetrahydrocitral and citronellal give the corresponding amides in yields of 70 and 50% respectively. In the latter case much charring occurs, some citronellal is produced, and it would appear that undesirable interaction takes place between the catalyst and the ethylenic linkage present in the aldoxime. This effect is still more pronounced with the doubly unsaturated citraloxime, the yields of amide being usually only about 40%. Attempts to eliminate side reactions by the use of solvents did not appear promising, much smaller conversions being obtained in boiling alcoholic and toluene solutions.

No amide of geranic acid has hitherto been described in the literature. The product of the above isomerisation was an oil, but it readily deposited some crystalline *geranamide*-I, m. p. 69—70°, from light petroleum solution. The material remaining in the mother liquors was originally partially resolved into its components by fractional distillation, but this method was laborious and extremely inefficient. Chromatography on alumina readily effected a separation of the amide mentioned above from an isomeric *geranamide*-II, m. p. 63—64°, and a repetition of the process on the liquid intermediate fraction resulted in almost complete resolution of the mixture.

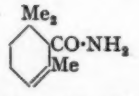
In the past the long-debated problem of the *iso*propylidene (CMe_2:) or *iso*propenyl (CH_2:CMe·) structures of members of the terpene group has usually been complicated both by the non-crystalline nature of the open chain terpenes, and by the existence of geometrical isomerides. The isolation of these two crystalline geran-

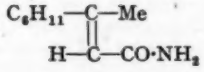
CMe_2:CH·CH_2·CH_2·CMe:CH·CO·NH_2 (I.)

CH_2:CMe·CH_2·CH_2·CH_2·CMe:CH·CO·NH_2 (II.)

amides is thus of considerable interest and four structural possibilities for these compounds had to be considered, *i.e.*, the *iso*propylidene and *iso*propenyl forms (I) and (II) and their respective geometrical isomerides.

Both geranamides were found to exhibit light absorption maxima at 2190 A., as would be expected of αβ-unsaturated amides; on refluxing with 2N-sulphuric acid, the known α-*cyclo*geranamide (III), m. p. 120—121°, was obtained in excellent yield from each isomer. From ozonolysis experiments, acetone 2 : 4-dinitro-

(III.) 



(IV.)

phenylhydrazone was isolated in identical yields of 84%;* in each case a trace (*ca.* 3%) of formaldehyde, estimated as the dimedon derivative, was also produced. The two amides must therefore be geometrical isomerides of structure (I), and it seems probable that, since citral is believed to consist mainly of the *cis*-isomer, citral-*a*, the more abundant geranamide-I may also be regarded as the *cis*-isomer (partial structure, IV). The light absorption intensities at the 2190 A. maxima of the two isomers are practically identical, no interconversions on irradiation are detectable, and differentiation on this basis is impossible. According to Henri and Errara (*Compt. rend.*, 1925, **180**, 2049) *trans*-isomers absorb more strongly than *cis*-isomers, but exceptions are known (Bruylants, *Bull. Acad. roy. Belg.*, 1927, **13**, 767; see also Castille, *ibid.*, 1930, **16**, 817).

It was hoped that, by hydrolysis of the individual geranamides, stereochemically pure samples of geranic acid might be obtained. With the boiling 10% alcoholic potassium hydroxide necessary for hydrolysis at a reasonable rate, isomerisation apparently occurs, giving an equilibrated geranic acid mixture from each isomer (cf. Bennett, Ramage, and Simonsen, *J.*, 1940, 418). From an incomplete hydrolysis of geranamide-I with 5% alkali, non-crystalline neutral material was recovered, indicating that isomerisation of the amide itself probably occurs under these conditions.

In view of the fact that the ozonolysis evidence cited above indicated that the isomeric geranamides both possess the *iso*propylidene configuration, further studies of these oxidation experiments were made. No variations in the yields were observed under different conditions and a similar (3%) yield of formaldehyde was obtained on ozonolysis of the saturated tetrahydrogeranamide for an equivalent time. It has long been known that saturated compounds are slowly attacked by ozone (Blair and Wheeler, *J. Soc. Chem. Ind.*, 1922, **41**, 303; 1924, **43**, 289; Briner and Meier, *Helv. Chim. Acta*, 1929, **12**, 529). Varying proportions of formaldehyde are produced on ozonolysis of terpenoid compounds, and the necessity and significance of quantitative determinations have been emphasised by Clemo and Macdonald (*J.*, 1935, 1294). More recently Stoll and Rouvé (*Helv. Chim. Acta*, 1944, **27**, 950), as a result of detailed investigations on the ozonolysis of ethyl oleate, have obtained evidence of the occurrence of oxidation of terminal carbon atoms. It is clear that the small amounts of formaldehyde produced in the present instance arise in all probability from the oxidation of terminal or side-chain methyl groups and have little significance in so far as evidence for the existence of the geranamides in the *iso*propenyl form (II) is concerned.

Experimental.

Rearrangement of Citronellaloxime to Citronellamide.—The oxime, obtained from citronellal and hydroxylamine acetate in aqueous methyl alcohol, had b. p. 95—97°/4 mm., $n_D^{17°}$ 1·4750 (Semmler, *Ber.*, 1893, **26**, 2255, gives b. p. 135—136°/14 mm., n_D 1·4763). A mechanically stirred mixture of citronellaloxime (20 g.) and Raney nickel (*ca.* 3 g.) was heated in a bath at 100—105° for 2 hours. After dilution with ether, the catalyst was removed by filtration through activated alumina, the ether was evaporated, and the residue crystallised from light petroleum (b. p. 40—60°). This gave the amide (8·1 g.) in large plates, m. p. 81·5—82·5°, a further quantity (1·9 g.) being obtained by distillation (b. p. 160—165°/16 mm.) of the material contained in the mother liquors (Wallach, *Annalen*, 1897, **296**, 125, and Tiemann, *Ber.*, 1898, **31**, 2902, give m. p. 82—83°).

Tetrahydrogeranamide from Tetrahydrocitraloxime.—A solution of citral (50 g.) in alcohol (350 c.c.) was shaken with hydrogen, under 11 atmospheres pressure, and palladium on calcium carbonate (25 g.; 10%) until absorption ceased (cf. Paal, D.R.P. 298,193; Rydon, *J.*, 1939, 1544). This gave tetrahydrocitral (30 g.), b. p. 82—84°/15 mm., $n_D^{17°}$ 1·4285, giving no colour with tetranitromethane. The semicarbazone had m. p. 88—88·5° [for *d*-tetrahydrocitral, Sabetay and Bléger (*Bull. Soc. chim.*, 1928, **43**, 843) give $n_D^{17°}$ 1·4273, semicarbazone, m. p. 78—79°; Suzucki (*Chem. News*, 1929, **139**, 153) gives $n_D^{21°}$ 1·4253, semicarbazone, m. p. 78°. Rupe and Giesler (*Helv. Chim. Acta*, 1928, **11**, 665) report that the semicarbazone of *dl*-tetrahydrocitral has m. p. 92—93°]. The oxime, prepared in the usual way, had b. p. 101—102°/4 mm., $n_D^{18°}$ 1·4531.

A mixture of tetrahydrocitraloxime (7·8 g.) and Raney nickel (*ca.* 1 g.) was stirred and heated in a bath at 110—120° for 2 hours. The product was freed from catalyst as described above; crystallisation from light petroleum (b. p. 60—80°) gave tetrahydrogeranamide (5·6 g.) in large glistening plates, m. p. 108—109° (Wallach, *Annalen*, 1897, **296**, 128, gives m. p. 108—109°).

Isomeric Geranamides from Citraloxime.—The oxime, prepared in aqueous methyl alcohol with hydroxylamine acetate, had b. p. 110—114°/4 mm., $n_D^{18°}$ 1·5186 (Tiemann and Semmler, *Ber.*, 1893, **26**, 2716, give b. p. 143—145°/12 mm., $n_D^{20°}$ 1·5143). A well stirred mixture of citraloxime (20 g.) and Raney nickel (*ca.* 3 g.) was heated in a bath at 115—120°

* The use of the iodometric method of acetone estimation as developed by Kuhn and Roth (*Ber.*, 1932, **65**, 1284) gives higher yields; in this case they would probably be over 95%.

for 2 hours. The catalyst was separated as described above; its complete removal is absolutely essential, otherwise extensive decomposition occurs on distillation. The product was distilled giving citral, b. p. 70—80°/4 mm., citraloxime, b. p. 110—120°/4 mm., and then a mixture of isomeric geranamides (9·9 g.) as a colourless oil, b. p. 130—132°/4 mm. An attempt to moderate the reaction by carrying it out in boiling toluene (80 c.c.) gave only 3·8 g. of the geranamide mixture.

On dissolving the mixed amides (38 g.) in light petroleum (35 c.c.; b. p. 40—60°) and keeping at 0° for 20 hours, *geranamide*-I (6·7 g.) separated in long needles, m. p. 69—70° (Found: C, 71·85; H, 10·25; N, 8·75. $C_{10}H_{17}ON$ requires C, 71·95; H, 10·25; N, 8·4%). Light absorption in alcohol: Maximum, 2190 A.; $\log \epsilon = 4·19$.

The mother liquors were evaporated, the residue was dissolved in light petroleum (300 c.c.; b. p. 60—80°) and adsorbed on a 75 × 1·5 cm. column of "Birlec" alumina. Two faint yellow bands were observed at the bottom of the column. Elution was effected with benzene, 50 c.c. portions of eluate being collected and evaporated to dryness. From the early fractions an oil (*ca.* 5 g.), probably citraloxime, was obtained, but after the yellow bands had been washed off the residue solidified readily on standing. Elution with benzene was continued until the material being eluted failed to crystallise. The solid fractions so far obtained were combined and crystallised from light petroleum (b. p. 40—60°) to give *geranamide*-II (2·6 g.) as large glistening plates, m. p. 63—64° (Found: C, 71·7; H, 10·1. $C_{10}H_{17}ON$ requires C, 71·95; H, 10·25%). Light absorption in alcohol: Maximum, 2190 A.; $\log \epsilon = 4·21$.

Elution with benzene was continued and eventually the material removed from the column again crystallised on standing. A benzene–chloroform mixture (1 : 1) was later employed. The combined solid fractions, on crystallisation from light petroleum (b. p. 40—60°), gave 8·5 g. of geranamide-I, m. p. 69—70°.

The intermediate non-crystallising portions were combined and rechromatographed giving further quantities of the pure isomers, the final yields from 38 g. of mixed amides being 21·4 g. of geranamide-I and 5·1 g. of geranamide-II.

Ozonolysis of Geranamide-I.—Geranamide-I (1·0 g.) was dissolved in "AnalaR" acetic acid (40 c.c.) (on which a completely satisfactory blank determination had been carried out) and ozonised oxygen was passed in until ozonolysis was complete (5 hours), the issuing gases being passed into water. The acetic acid solution was mixed with the wash water and the resulting solution was divided into two equal portions. (*a*) Water (50 c.c.) was added and, after being warmed until a clear solution was obtained, the mixture was distilled in steam. The steam distillate was collected in 5 c.c. portions, each of which was treated with 2 : 4-dinitrophenylhydrazine sulphate. The first two fractions yielded a heavy orange precipitate, which on crystallisation from aqueous methyl alcohol gave acetone 2 : 4-dinitrophenylhydrazone (600 mg.; 84% of theoretical), m. p. 123—125°, undepressed on admixture with an authentic specimen. (*b*) The second portion was dropped into boiling water (50 c.c.) and zinc dust (7 g.) in a distillation flask. The volatile products were passed into a saturated aqueous solution of dimedon and the solution was kept overnight. The precipitate of fluffy needles (30 mg.; 3% of theoretical) was separated and crystallised from aqueous methyl alcohol, from which the formaldehyde dimedon derivative crystallised in long needles, m. p. 187—188°, undepressed on admixture with an authentic specimen.

A similar yield of the formaldehyde dimedon derivative was obtained on ozonolysis of tetrahydrogeranamide under identical conditions.

Ozonolysis of Geranamide-II.—The amide (1·0 g.) was treated with ozonised oxygen exactly as described above for the first isomer. The yield of acetone 2 : 4-dinitrophenylhydrazone was 600 mg. (84%), and that of the formaldehyde dimedon derivative was 40 mg. (4% of theory).

Alkaline Hydrolysis of the Amides.—(a) Geranamide-I (3 g.) was refluxed with alcoholic potassium hydroxide (60 c.c.; 10%) for 16 hours giving geranic acid (2·8 g.), b. p. 90—92°/2 mm. This was split arbitrarily on a second distillation into several fractions which had $n_D^{20°}$ in the range 1·4782—1·4792 (Barbier and Bouveault, *Bull. Soc. chim.*, 1896, **15**, 1002, give b. p. 157·5°/18 mm., n_D 1·4836; Bennett, Ramage, and Simonsen, *loc. cit.*, give the following values for the acid from different sources: $n_D^{25°}$ 1·4839, 1·4725—1·4783, 1·4988). Attempts to convert the geranic acid into pure crystalline derivatives were unsuccessful.

Hydrolysis of geranamide-I (2 g.) with boiling alcoholic potassium hydroxide (40 c.c.; 5%) was incomplete after 16 hours and the recovered neutral portion (1·1 g.) could not be induced to crystallise.

(b) When geranamide-II (1 g.) was hydrolysed by boiling with alcoholic potassium hydroxide (20 c.c.; 10%) for 16 hours, the geranic acid (0·9 g.) so obtained had b. p. 150°/18 mm., $n_D^{20°}$ 1·4779, and failed to yield any crystalline derivatives.

Cyclisation of the Isomeric Geranamides.—(a) Geranamide-I (1·9 g.) was heated under reflux with sulphuric acid (25 c.c.; 2N.) for 16 hours; on cooling, the insoluble oil crystallised. The product was separated with ether and on crystallisation from aqueous methyl alcohol gave *α-cyclo*geranamide (1·5 g.; 80%), m. p. 120·5—121°, undepressed on admixture with an authentic specimen (Barbier and Bouveault, *Bull. Soc. chim.*, 1896, **15**, 1003, and Bouveault, *ibid.*, 1910, **7**, 352, give m. p. 120—121°).

(b) Geranamide-II (100 mg.) under similar conditions gave 80 mg. of *α-cyclo*geranamide, m. p. 120—121°, undepressed on admixture with an authentic specimen.

The authors thank the Colonial Products Research Council for financial support which rendered this work possible.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, S.W. 7. [*Received, December 21st*, 1945.]

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122. *Molecular Rearrangements. Part V.* A Case of a Thermal Reversible α-Diketone–γ-Lactone Rearrangement. Some Experiments with Vulpinic Acid and Related Compounds.*

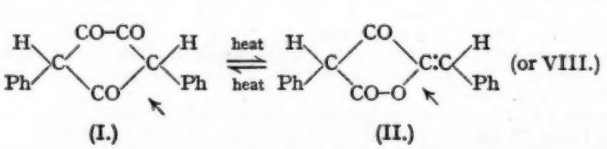
By ALEXANDER SCHÖNBERG and ALY SINA.

In the molten state oxalyl dibenzyl ketone (I) and its isomer (II) form an equilibrium mixture. The naturally occurring vulpinic acid (VI) was degraded *via* pulvinic acid (V) into (II) by using a copper chromite catalyst. The action of *o*-phenylenediamine on vulpinic acid and related substances was investigated; it led to the formation of a condensation product which on hydrolysis with alcoholic potassium hydroxide yielded 2-benzylbenziminazole (compare scheme A).

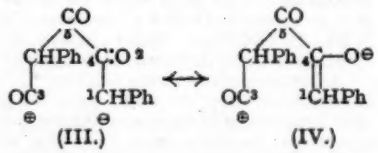
* Cf. Schönberg and co-workers, *Ber.*, 1930, **63**, 178; *Annalen*, 1930, **483**, 107; *Ber.*, 1931, **64**, 1390; 1933, **66**, 250.

(A) REVERSIBLE α-diketone–γ-lactone rearrangements are already known as in the case of benzil-*o*-carboxylic acid (Hantzsch and Schwiete, *Ber.*, 1916, **49**, 220), but this is an example of simple ring-chain tautomerism:

Claisen and Ewan (*Annalen*, 1894, **294**, 276) found that, at about 228°, oxalyl dibenzyl ketone (1 : 3-diphenyl-*cyclo*pentan-2 : 4 : 5-trione) is rapidly converted by heat into its isomer (yield 75%), which, they stated, could not be reconverted by heat into the original ketone. According to our observations, this thermal rearrangement involves equilibrium between the homocyclic ring and a γ-lactone, (I) ⇌ (II). When (II) is heated above



(I.) (II.) (or VIII.)



(III.) (IV.)

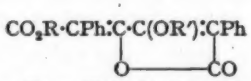
270° the resulting equilibrium mixture of (I) and (II) has its equilibrium disturbed by the removal of (I) by sublimation. It is thus possible to obtain (I) from (II) in excellent yield.

To explain this thermal change the following theory is advanced: Ionic fission of the bonds marked with an arrow in (I) and (II) affords a "zwitterion" which would be a resonance hybrid of structures (III) and (IV); rotation about the C^5–C^4 bond can then bring into close proximity either atoms C^1 and C^3 (to yield I) or O^2 and C^3 (to yield II).

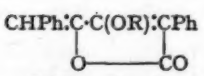
(B) One of the most important derivatives of the so-called "*iso*oxalyl dibenzyl ketone" (II) is pulvinic acid (V), the methyl ether of which, vulpinic acid (VI), occurs in nature. The following experiments have been made with this acid and related compounds.

(a) *Degradation of pulvinic acid* (V) *to* iso*oxalyl dibenzyl ketone.* Hitherto, this degradation had not been achieved, Claisen and Ewan (*loc. cit.*, p. 295) having failed to effect it, but we have now done so by heating pulvinic acid with copper chromite and quinoline, thus giving additional proof of the relationship between the acid and the ketone.

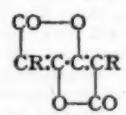
(b) *Action of diazomethane on pulvinic acid and* iso*oxalyl dibenzyl ketone.* In both cases a vigorous reaction took place, the methyl ethers of vulpinic acid and *iso*oxalyl dibenzyl ketone, (VII) and (IX) respectively, being obtained.



(V), R = R′ = H (pulvinic acid).
(VI), R = Me; R′ = H (vulpinic acid).
(VII), R = R′ = Me.

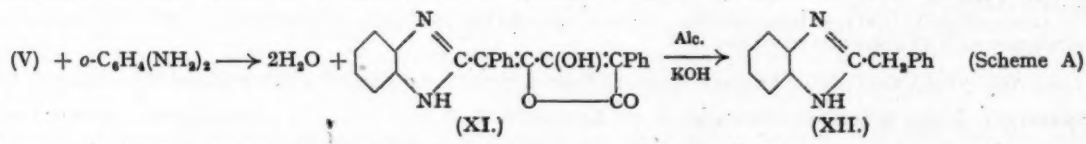


(VIII), R = H.
(IX), R = Me.



(X*a*), R = Ph.
(X*b*), R = *p*-C_6H_4OMe.

(c) *Action of o-phenylenediamine on pulvinic acid, vulpinic acid, pulvinic acid dilactone* (X*a*) *and* pp′-*dimethoxy-pulvinic acid dilactone* (X*b*). This action leads in the first three cases to the benziminazole *derivative* (XI), an orange substance soluble in sodium hydroxide. Similarly, from *o*-phenylenediamine and *pp′*-dimethoxy-



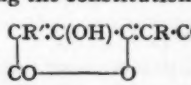
(Scheme A)

(XI.) (XII.)

pulvinic acid dilactone (X*b*), the pp′-*dimethoxy*-derivative of (XI) was obtained. By the action of diazomethane or methyl sulphate, (XI) is converted into a yellow O-*methyl ether*.

When (XI) was treated with alcoholic potassium hydroxide, a colourless product was obtained which proved to be 2-benzylbenziminazole (XII), and this, when treated with selenium (precipitated) in the presence of oxygen, yielded benzoic acid.

This new degradation method of vulpinic acid and related compounds (compare scheme A) should be of value in ascertaining the constitution of asymmetrically substituted derivatives of vulpinic acid. For example,



(XIII*a*), R = Ph; R′ = *p*-C_6H_4·OMe.
(XIII*b*), R = *p*-C_6H_4·OMe; R′ = Ph.

the synthesis of the naturally occurring pinastrinic acid could lead to (XIII*a*) or (XIII*b*). The benziminazole derivative of pinastrinic acid, prepared according to scheme A, should yield, on alkaline hydrolysis, 2-benzyl-benziminazole (XII) if the proposed formula (XIII*a*) for pinastrinic acid is correct (cf. Asano and Kameda, *Ber.*, 1934, **67**, 1522); otherwise 2-(*p*-methoxybenzyl)benziminazole would be obtained.

Experimental.

(A) *Transformation of* iso*Oxalyl Dibenzyl Ketone* (II) *into Oxalyl Dibenzyl Ketone* (I).—0·5 G. of (II) was heated under 40 mm., or in a stream of dry carbon dioxide, at 271° (bath temp.). [It is important that the sublimate of (I) which is formed during this process should be protected from heat, otherwise it melts and is reconverted into (II); therefore it is advisable to work with a metal-bath the surface of which is covered with asbestos.] Nearly the whole sublimed into the cooler parts of the reaction vessel, and the sublimate proved to be oxalyl dibenzyl ketone, m. p. 192° not depressed by admixture with an authentic sample (Found: C, 77·1; H, 4·7. Calc. for $C_{17}H_{12}O_2$: C, 77·3; H, 4·6%).

The quinoxaline derivative, prepared from the sublimate and *o*-phenylenediamine, had m. p. 255° not depressed by admixture with an authentic sample (cf. Chakravarti, *Centr.*, 1926, I, 120). We found that it is unaffected by an ethereal solution of diazomethane, showing that it has no tendency to react in the enolic form.

Detection of oxalyl dibenzyl ketone in the melt of iso*oxalyl dibenzyl ketone.* The *iso*-ketone (0·5 g.) was put in a sealed tube and completely immersed in a boiling ethyl cinnamate bath, in order to avoid sublimation of oxalyl dibenzyl ketone on the cooler parts of the vessel. After the substance had melted, it was left in the boiling bath for a further 5 minutes and then taken out.

(i) Colour reaction. An alcoholic solution of the melt gives with alcoholic ferric chloride a brownish-green coloration characteristic of oxalyl dibenzyl ketone; *iso*oxalyl dibenzyl ketone gives no colour with the same reagent (cf. Claisen and Ewan, *loc. cit.*, p. 252).

(ii) Isolation. The cooled melt was extracted with boiling benzene in which oxalyl dibenzyl ketone is more soluble than the *iso*-ketone. From this extract, after several crystallisations from benzene, a small amount of oxalyl dibenzyl ketone was obtained (identified by m. p., mixed m. p. with an authentic sample, and the above colour reaction).

Action of heat on oxalyl dibenzyl ketone in a closed vessel. The reaction was carried out as described above for the *iso*-ketone. The substance first melted, then resolidified, and then remelted when it was heated for a further 5 minutes. The cooled crystalline melt had m. p. 248° and consisted principally of the *iso*-ketone (m. p. 253°). To prove the presence of oxalyl dibenzyl ketone in the melt, it was treated with hot benzene, as described above, and this ketone was obtained (identified by mixed m. p. and ferric chloride reaction).

Even after prolonged heating (one hour) in a boiling ethyl cinnamate bath, the presence of oxalyl dibenzyl ketone could be proved by the ferric chloride reaction, and complete conversion of (I) into (II) could not be effected. On more prolonged heating, the *iso*-ketone resinified.

Oxidation of iso*Oxalyl Dibenzyl Ketone.*—This ketone (15 g.) was dissolved in 200 c.c. of 3% aqueous sodium carbonate, and the mixture diluted to 400 c.c. and cooled to 0°. Then, with continuous stirring, an ice-cold solution of potassium permanganate (18 g. in 200 c.c. of water) was added gradually, the mixture being kept at 0°. After 2 hours the mixture was filtered, and the residue washed with ether. The filtrate was extracted with ether repeatedly, the ethereal extracts combined, and the ether driven off, leaving an oily residue (6 g.). 2 G. of this residue were treated with an aqueous solution of phenylhydrazine acetate in the usual manner, and 1·3 g. of crystalline benzaldehyde phenylhydrazone were obtained (cf. Claisen and Ewan, *loc. cit.*, p. 282).

(B) *Condensation of Vulpinic Acid* (VI) *with* o*-Phenylenediamine Hydrochloride.*—Vulpinic acid (Volhard, *Annalen*, 1894, **282**, 13) (0·5 g.) and *o*-phenylenediamine hydrochloride (0·35) g. were mixed with *N*-dimethylaniline (15 c.c.), and the whole boiled under reflux for 2 hours. After cooling, the solution was poured into dilute hydrochloric acid, and the mixture well stirred. The separated solid was washed with dilute hydrochloric acid and then with distilled water. The dry reaction product crystallised from ethyl acetate as orange needles, m. p. 312° (Found: C, 75·5; H, 4·4; N, 7·7. $C_{21}H_{16}O_3N_2$ requires C, 75·8; H, 4·2; N, 7·4%). *βγ-Dihydroxy-αδ-diphenyl-δ-2-benziminazolyl-*$\Delta^{\alpha\gamma}$*-pentadienoic acid lactone* (XI) is soluble in dilute aqueous potassium hydroxide, giving a yellow solution from which the original substance is precipitated on acidification with dilute hydrochloric acid. It is difficultly soluble in benzene and alcohol, but soluble in hot ethyl acetate and glacial acetic acid.

Condensation of Pulvinic Acid (V), *Pulvinic Acid Dilactone* (X*a*), *and* pp′*-Dimethoxypulvinic Acid Dilactone with* o*-Phenylenediamine.*—Pulvinic acid (Volhard, *loc. cit.*, p. 14) or its dilactone, similarly treated, afford the compound (XI), m. p. 314° not depressed by admixture with the specimen obtained above [Found, from (V): C, 75·5; H, 4·3; N, 7·4. Found, from (X*a*): C, 75·4; H, 4·3; N, 7·7%].

pp′-Dimethoxypulvinic acid dilactone (Kögl, *Annalen*, 1928, **465**, 254), similarly treated, afforded the pp′*-dimethoxy*-derivative of (XI), deep reddish-orange crystals, m. p. 334° after crystallisation from ethyl acetate (Found: C, 70·7; H, 4·5; N, 6·1. $C_{25}H_{20}O_5N_2$ requires C, 70·9; H, 4·6; N, 6·4%), difficultly soluble in alcohol, but soluble in hot ethyl acetate and hot glacial acetic acid.

Hydrolysis of (XI) *with alcoholic potassium hydroxide.* 1 G. of (XI) was refluxed with 20 c.c. of alcoholic potash (4 g. of potassium hydroxide in 40 c.c. of 95% alcohol) for 3 hours. Colourless crystals of potassium oxalate separated during the hydrolysis. The mother-liquor, after filtration, was acidified with dilute hydrochloric acid and concentrated to a small volume; an oil separated, which solidified on standing in ice. This was collected, washed with distilled water until free from inorganic salts, and crystallised twice from dilute alcohol (charcoal). On dissolving these crystals in the minimum of distilled water and making the solution alkaline with aqueous potassium hydroxide, a white milky precipitate was formed which soon set to colourless needles; recrystallised from dilute alcohol, these had m. p. 189° not depressed when mixed with an authentic sample of 2-benzylbenziminazole (Walther and Pulawski, *J. pr. Chem.*, 1899, **59**, 253) (Found: C, 80·8; H, 5·8; N, 13·4. Calc. for $C_{14}H_{12}N_2$: C, 80·8; H, 5·8; N, 13·4%).

Oxidation of 2-Benzylbenziminazole with Oxygen in Presence of Selenium.—2-Benzylbenziminazole (0·4 g.) was intimately mixed with precipitated selenium (Kahlbaum) (8 g.), and heated in the bulb of a long-necked pyrolysis flask in a bath the temperature of which was gradually raised to 290°, a continuous stream of air being passed through. In the higher parts of the neck, benzoic acid sublimed (mixed m. p.).

Methylation of (XI).—(i) 0·5 G. of (XI) was dissolved in excess of dilute potassium hydroxide, and to the alkaline solution methyl sulphate (4 c.c.) was gradually added with shaking after each addition. The precipitate was collected, washed repeatedly with distilled water, then dried at the water-pump and finally crystallised from absolute alcohol. The O-*methyl ether* of (XI) formed yellow plates, m. p. 325°, difficultly soluble in alcohol, benzene, carbon tetrachloride and ethyl acetate, and insoluble in dilute cold sodium hydroxide solution (Found: C, 75·95; H, 4·9; N, 7·1. $C_{22}H_{18}O_3N_2$ requires C, 76·1; H, 4·6; N, 7·1%); no active hydrogen was found.

(ii) 0·5 G. of (XI) was finely pulverised, suspended in ether, treated with an ice-cold ethereal solution of diazomethane, and left on ice overnight; the yellow solid that separated was collected, washed with cold alcohol and then crystallised from hot methyl alcohol. The yellow crystals had m. p. 326° not depressed by admixture with the product obtained as in (i).

Prolonged treatment with excess of an ethereal solution of diazomethane in the cold failed to methylate either 2-benzyl- or 2-phenyl-benziminazole.

Action of Diazomethane on iso*Oxalyl Dibenzyl Ketone.*—0·5 G. of the ketone was methylated as above by diazomethane (from 10 g. of nitrosomethylurea); the crystals which separated on concentration of the solution, crystallised from methyl

alcohol, formed colourless crystals of *isooxalyl dibenzyl ketone methyl ether* (IX), m. p. 106° (Found: C, 77·7; H, 5·1. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·0%); no active hydrogen was found. (Cf. Kögl, *loc. cit.*, p. 256.)

Action of Diazomethane on Pulvinic Acid (V).—This acid, similarly treated, gave vulpinic acid methyl ether (VII), m. p. 142—143° after crystallisation from methyl alcohol (cf. Spiegel, *Annalen*, 1883, **216**, 16) (Found: C, 71·5; H, 4·9. Calc. for $C_{20}H_{16}O_5$: C, 71·4; H, 4·8%).

Decarboxylation of Pulvinic Acid.—Pulvinic acid (1 g.) was dissolved in freshly distilled dry quinoline (5 c.c.), and the solution heated (with mechanical stirring) in a boiling nitrobenzene bath for 15 minutes, during which copper chromite (*Org. Synth.*, **19**, 31) (0·8 g.) was gradually added in portions of 0·1 g. After cooling, the reaction mixture was poured into dilute hydrochloric acid and stirred for 10 minutes. The solid was filtered off, washed with distilled water, and then extracted repeatedly with boiling dilute potassium carbonate solution to dissolve *iso*oxalyl dibenzyl ketone. The filtered aqueous extract was washed three times with ether in a separating funnel, freed from ether, acidified with dilute hydrochloric acid, and the resulting yellow precipitate was collected, pressed on a porous plate, and crystallised from toluene containing a small amount of glacial acetic acid. Yellow crystals were formed, m. p. 253° not depressed by admixture with an authentic specimen of *iso*oxalyl dibenzyl ketone.

FOUAD I UNIVERSITY, ABBASSIA, CAIRO. [*Received, March 1st*, 1945.]

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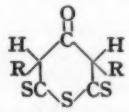
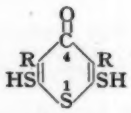
123. *Organic Sulphur Compounds. Part XXIX. Experiments with 1-Thia-γ-pyrones. Thermal Rearrangement of 1-Thia-γ-pyrone Derivatives into the Isomeric 1-Thia-α-pyrone Derivatives.*

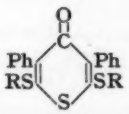
By ALEXANDER SCHÖNBERG and (MISS) WAFIA ASKER.

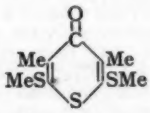
2 : 6-Bisalkylthio-1-thia-γ-pyrones are stable towards acids, but yield on alkaline hydrolysis thio-ethers containing one triple and one double bond (see scheme A). Some 1-thia-γ-pyrones were converted into the corresponding 4-thio-1-thia-γ-pyrones by the action of thionyl chloride followed by that of thioacetic acid (see scheme B). 2 : 6-Dithio-3 : 5-diphenyl-1-thia-γ-pyranone (I, R = Ph) on heating yields the thionaphthen derivative (IX); in addition, another product of pyrolysis was formed for which formulæ (X) and (XII) are discussed. A thermal rearrangement by which 4-thio-1-thia-γ-pyrone derivatives were irreversibly transformed into the isomeric 2-thio-1-thia-α-pyrone derivatives was observed (see scheme C) and its mechanism is discussed. It was found that some 4-thio-1-thia-γ-pyrone derivatives (*e.g.*, XIV) and also thiobenzophenone and its derivatives are easily converted into the corresponding ketones (*e.g.*, benzophenone) by the action of thionyl chloride followed by hydrolysis (see scheme D). 3 : 5-Diphenyl-1-thia-γ-pyrone (XIX) was obtained by a dehydrogenating process using phorphorus pentachloride as the agent.

THE orange substances obtained by the action of carbon disulphide on ketones of the general type $CH_2R{\cdot}CO{\cdot}CH_2R$ in the presence of alkali have the constitution (I); they exhibit thiono–thiol tautomerism and form colourless or almost colourless compounds which are derivatives of 2 : 6-dithiol-1-thia-γ-pyrone (II) (Schönberg and Asker, J., 1945, 198). Both groups of substances are easily available and have been investigated in some detail.

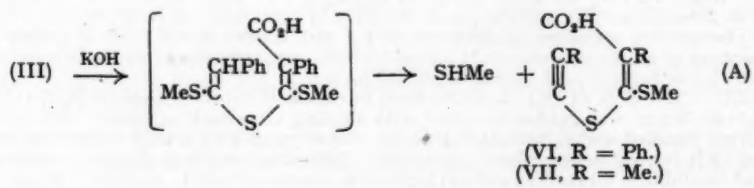

(I.)


(II.)


(III, R = Me.)
(IV, R = Et.)


(V.)

(a) *Action of Acids and of Alkalis on Derivatives of* (II).—Substances (III) and (V), heated under reflux with acetic acid saturated with hydrogen chloride, were recovered unchanged, but on treatment with aqueous-alcoholic potassium hydroxide the ring was opened, the acids (VI) and (VII), respectively, being obtained:

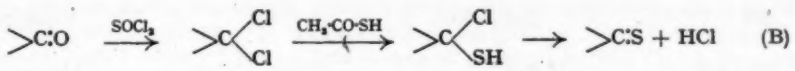

(VI, R = Ph.)
(VII, R = Me.)

The *acid* (VI) is bright yellow; it is soluble in aqueous alkalis and is reprecipitated unchanged on acidification. It reacts with diazomethane to form a *methyl* ester, insoluble in alkalis but readily hydrolysed to the acid by boiling alkalis or acids. The *acid* (VII) is similar.

This ring scission is of value in that it affords thio-ethers containing a triple and a double bond which are not otherwise readily available.

(b) *Action of Thionyl Chloride followed by Thioacetic Acid on* (III) *and* (IV).—When ketones which are

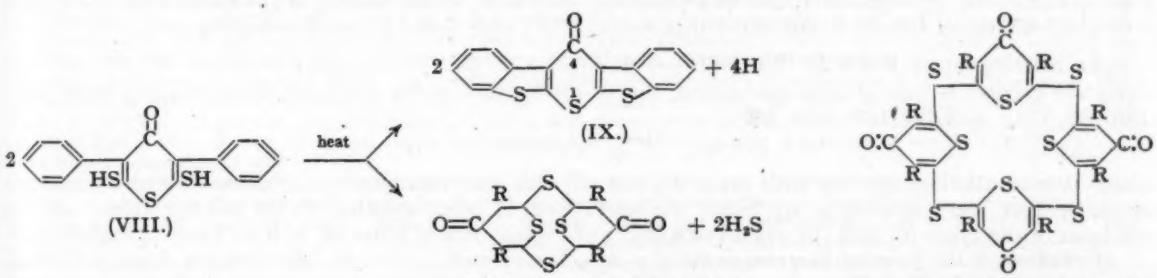
not capable of forming enols (*e.g.*, benzophenone and xanthone) are treated with thionyl chloride followed by thioacetic acid, the corresponding thioketones are formed (Schönberg, *Ber.*, 1928, **61**, 1375) : *



(B)

By this means we have converted the ketones (III) and (IV) into the corresponding *thioketones* (XIV) and (XV). These substances are brilliantly coloured, showing the dichroism characteristic of substances of similar constitution, *e.g.*, 2 : 6-diphenyldithiopyrone (Arndt *et al.*, *Ber.*, 1925, **58**, 1644). With solid mercuric chloride both (XIV) and (XV) show the colour reaction described for xanthione and 2 : 6-dimethyl-4-thiopyrone (Schönberg, *Ber.*, 1925, **58**, 1794).

(c) *Pyrolysis of* 2 : 6-*Dithio*-3 : 5-*diphenyl- and* -3 : 5-*dimethyl*-1-*thia*-γ-*pyranone* (I, R = Ph or Me).—The ketone (I, R = Ph), or its thiol form (VIII), on pyrolysis yields two substances. One of these, namely, 2 : 3-6 : 5-*dithionaphtheno*-1-*thia*-γ-*pyrone* (IX) is a result of dehydrogenation (possibly under the influence of the elementary sulphur formed during pyrolysis); owing to its low solubility its molecular weight could not be determined, but it is nevertheless beyond doubt, since that of one of its derivatives, namely, 4 : 4-di-*m*-tolyl-2 : 3-6 : 5-dithionaphtheno-1-thia-γ-pyran (see following paper), has been established. The second

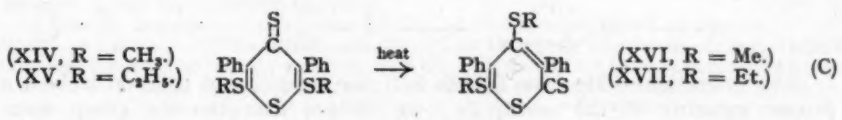


(VIII.) (IX.) (X, R = Ph.) (XI, R = Me.) (XII, R = Ph.) (XIII, R = Me.)

product of pyrolysis, probably (X) or (XII), is formed with elimination of hydrogen sulphide; as it is very difficultly soluble in all the usual solvents, its molecular weight could not be ascertained.

The methyl analogue of (I, R = Ph) yields on pyrolysis only one organic *product*, probably (XI) or (XIII).

(d) *Thermal Rearrangements of* γ-*Thiopyrones to* α-*Thiopyrones.*—Such rearrangements were observed when 2 : 6-*bismethylthio*-4-*thio*-3 : 5-*diphenyl*-1-*thiapyrone* (XIV) and its *ethyl* analogue (XV) were heated above their m. p., either alone or in the presence of solvents :

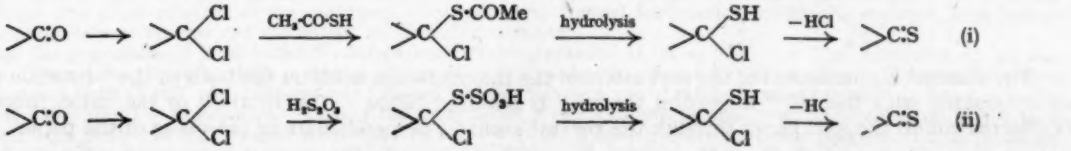


(C)

The structure of the *products* (XVI) and (XVII) follows from their properties and method of formation.

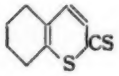
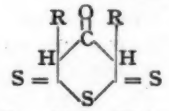
4-Thio-1-thiapyrones dissolve with a blue or green colour in benzene (see Arndt *et al.*, *loc. cit.*; Schönberg *et al.*, *Ber.*, 1928, **61**, 1382), but (XVI) and (XVII) form red solutions in benzene. As many substances containing, as do (XVI) and (XVII), the grouping A–S–CS–C (A = univalent group) (see p. 606) also give red solutions, this is evidence in support of the constitutions assigned to (XVI) and (XVII). In accordance with

* Gleu and Schaarschmidt (*Ber.*, 1939, **72**, 1251) have published a method (cf. ii) of converting the carbonyl into the thiocarbonyl group remarking that it shows " eine offensichtliche Parallele zu einer Methode von Schönberg (*Ber.*, 1928, **61**, 1375)." According to them, Schönberg's method is represented by (i), but since the action of water is



not necessary, it is correctly represented by (B). When thioketones are prepared by a method using hydrolysis (see ii), there is always the possibility that some of the corresponding ketone is formed in addition. Ketones and the corresponding thioketones are extremely difficult to separate by crystallisation, and for this reason the above method (B) was developed to avoid the use of a hydrolysing agent.

these structures, (XVI) and (XVII) do not show the behaviour of thioketones, for they are practically unchanged when treated with oxalyl chloride or thionyl chloride followed by water. If these substances,

Me·C(:S)·SH	Red-yellow	Ph·C(:S)·SH	Violet-red
$[(\alpha)C_{10}H_7\cdot CS\cdot S\cdot]_2$	Red	$CHPh_2\cdot C(:S)\cdot SPh$	Orange
	Red		Orange-red

(R = Me or Ph.)

like their progenitors, were thioketones, replacement of one sulphur atom by oxygen would have taken place:

$$>C{:}S \xrightarrow{SOCl_2 \text{ or } (COCl)_2} >C(Cl)Cl \xrightarrow{H_2O} >C{:}O \qquad (D)$$

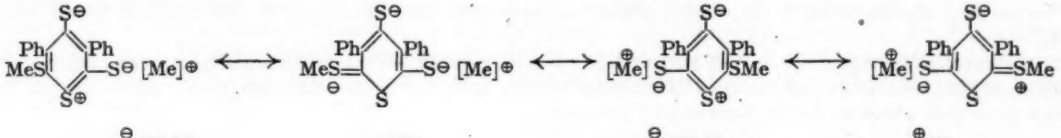
The ready replacement of the :CS group in thioketones according to (D) seems to be a general reaction; thiobenzophenone, *pp'*-dimethoxythiobenzophenone, xanthione, dithioflavone, 2 : 6-bisethylthio- (XV) and 2 : 6-bismethylthio-4-thio-3 : 5-diphenyl-1-thiapyrone (XIV) were found to react according to (D).

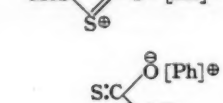
The rearrangement $R'\cdot CS\cdot CR''{:}CR'''\cdot SR \xrightarrow{heat} R'\cdot C(SR){:}CR''\cdot CR'''{:}S$ (cf. C) (R = alkyl; R', R'', R''' are univalent groups) is that of a pentad system, but resembles that of the triad system (Schönberg *et al.*, *Ber.*, 1930, **63**, 178; *Annalen*, 1930, **483**, 107):

$$CO(SR)_2 \xrightarrow{heat} C(OR)(SR)S \qquad (E)$$

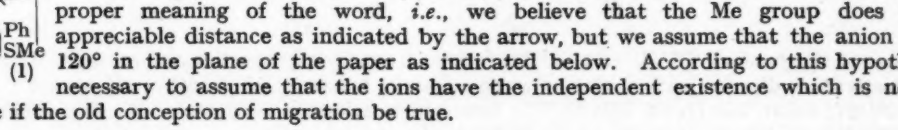
where R is an alkyl group. In both cases, (C) and (E), the rearrangements are irreversible and are brought about by heat, the migrating group before the rearrangement being attached to the sulphur atom. All the reactions of the types (C) and (E) yet investigated yield substances of lower m. p. from those of higher m. p.

Mechanism of the Thermal Rearrangement of γ- to α-Thiopyrones (C) *and of Thioncarbonic Acids to Esters of Thiolcarbonic Acids* (E).—These thermal isomerisations may be explained by assuming that at high temperatures ionic structures make a definite contribution to the mesomeric state. In both cases, the unusual stability of the organic anion may be explained by resonance stabilisation. Only a few of the possible structures are shown below:

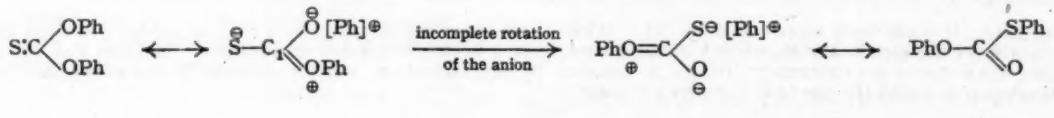




The migration of Me from S(1) to S(2) (see inset) is not believed to be a migration in the proper meaning of the word, *i.e.*, we believe that the Me group does not move an appreciable distance as indicated by the arrow, but we assume that the anion rotates about 120° in the plane of the paper as indicated below. According to this hypothesis, it is not necessary to assume that the ions have the independent existence which is necessary for a short time if the old conception of migration be true.

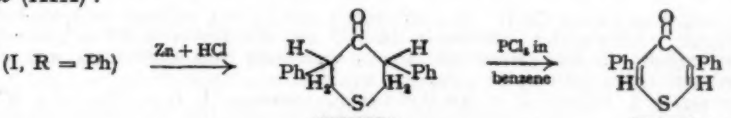


The thermal isomerisation of the aryl esters of the thioncarbonic acids on the basis of the " rotation theory " as contrasted with the old " migration theory " is pictured below. The rotation of the anion (about 120°) is effected round the axis going through the central atom C_1 perpendicular to the plane of the paper.



On the basis of the migration theory, it is difficult to explain why anions and cations, which are generally regarded as reactive, should not react with a solvent, and special theories have been advanced to explain this. When the rearrangement takes place in consequence of rotation, no reaction would be expected with the molecules of the solvent, as the electrically charged groups do not migrate in space and therefore do not collide with the molecules of the solvent; the concept of rotation has also led to the discovery of the reversible thermal rearrangement oxalyl dibenzyl ketone ⇌ *iso*oxalyl dibenzyl ketone (Schönberg and Aly Sina, this vol., p. 601).

(e) We have treated (XVIII) with phosphorus pentachloride in benzene solution and obtained 3 : 5-*diphenyl*-1-*thia*-γ-*pyrone* (XIX):



(XVIII.) (XIX.)

By a similar process Arndt, Nachtwey, and Pusch (*Ber.*, 1925, **58**, 1639) prepared 2 : 6-diphenyl-1-thia-γ-pyrone.

Experimental.

Action of Alcoholic Potassium Hydroxide on 2 : 6-*Bismethylthio*-2 : 6-*diphenyl*-1-*thia*-γ-*pyrone* (III).—The pyrone (1 g.) (Apitzsch, *Ber.*, 1904, **37**, 1607; 1905, **38**, 2891) was refluxed with alcoholic potash (1·5 g. KOH in 30 c.c. alcohol) for one hour. The solution was filtered when cold and acidified with dilute hydrochloric acid; a yellow amorphous substance was obtained, and a foul pungent odour evolved. After standing for 24 hours the substance was collected, washed with water, and dried on a porous plate; β-(*phenylacetylenylthio*)-β-*methylthio*-α-*phenylacrylic acid* (VI) then crystallised from toluene in light yellow crystals, m. p. 200° (Found: C, 66·45; H, 4·55; S, 19·2. $C_{18}H_{14}O_2S_2$ requires C, 66·3; H, 4·3; S, 19·6%). It gave an almost colourless solution with concentrated sulphuric acid and dissolved in cold aqueous potassium hydroxide; it was recovered unchanged after 6 hours' refluxing with a mixture of acetic acid (20 c.c.) and concentrated hydrochloric acid (10 c.c.).

Action of diazomethane on (VI). Diazomethane in ethereal solution, added to (VI), dissolved with a vigorous evolution of gases; the solution was kept at 0° for 24 hours, and the solvent then evaporated. The residue was crystallised from ligroin (b. p. 80—90°), and the *methyl* ester obtained in yellow plates, m. p. 153° (Found: C, 67·1; H, 4·5; S, 18·4. $C_{19}H_{16}O_2S_2$ requires C, 67·1; H, 4·7; S, 18·8%), soluble in concentrated sulphuric acid with a yellow colour, and insoluble in aqueous potassium hydroxide. The ester (1 g.), when dissolved in acetic acid (30 c.c.) and refluxed for 4 hours with hydrochloric acid (10 c.c.), gave light yellow crystals of the acid.

Action of Alcoholic Potassium Hydroxide on 2 : 6-*Bismethylthio*-3 : 5-*dimethyl*-1-*thia*-γ-*pyrone* (V).—The pyrone (1 g.) (Apitzsch, *loc. cit.*, 1905), when treated with alcoholic potash as for (III), afforded ultimately pale yellow crystals, m. p. 155° (from benzene). This *acid* (VII) (Found: C, 47·8; H, 5·3; S, 31·3. $C_8H_{12}O_2S_2$ requires C, 47·5; H, 4·9; S, 31·6%) behaved exactly like its analogue (VI). Its *methyl* ester, prepared by means of diazomethane, crystallised from ligroin (b. p. 60—70°) in colourless crystals, m. p. 81° (Found: C, 49·8; H, 5·51; S, 30·0. $C_9H_{12}O_2S_2$ requires C, 50·0; H, 5·6; S, 29·6%), insoluble in aqueous potassium hydroxide. Hydrolysis as above afforded the acid (VII).

Non-action of Alcoholic Potassium Hydroxide on 2 : 6-*Dithio*-3 : 5-*diphenyl*-1-*thia*-γ-*pyranone* (I, R = Ph).—The pyranone (2 g.) (Apitzsch, *locc. cit.*), refluxed with alcoholic potash (3 g. KOH; 40 c.c. alcohol) for 4 hours, afforded a red-brown solution with much yellow deposit. The mixture was cooled, filtered, and the filtrate acidified with dilute hydrochloric acid, giving unchanged (I, R = Ph). The solid was dissolved in water (easily soluble) and acidified, but the red crystalline deposit, after crystallisation from chloroform, proved to be (I, R = Ph); m. p. of both samples 163°, not depressed by admixture with an authentic specimen.

2 : 6-*Bismethylthio*-4-*thio*-3 : 5-*diphenyl*-1-*thiapyrone* (XIV).—2 : 6-Bismethylthio-3 : 5-diphenyl-1-thia-γ-pyrone (III) Apitzsch, *loc. cit.*) (3 g.) was refluxed with thionyl chloride (30 c.c.) for 10 hours. The excess of thionyl chloride was distilled off by aid of the pump, and the residual red oil was dissolved in dry benzene (40 c.c.) and refluxed for 6 hours with thioacetic acid (8 c.c.). The excess of benzene and thioacetic acid was distilled off, and on addition of ligroin (b. p. 30—50°) to the residue, the *thioketone* (XIV) was deposited in violet-green crystals; recrystallised from xylene, it had m. p. 252° (red melt) [Found: C, 61·0; H, 4·4; S, 34·9; *M* (Rast's method), 384. $C_{18}H_{16}S_4$ requires C, 61·2; H, 4·3; S, 34·4%; *M*, 372]. It dissolved in hot benzene with a green colour, was difficultly soluble in ether and very sparingly soluble in acetone; the crystals when pressed gave a green powder. It was insoluble in aqueous potassium hydroxide and did not react with diazomethane; it was recovered unchanged when refluxed (1 g.) with copper bronze (4 g.) for 5 hours in xylene solution (30 c.c.). When mercuric chloride crystals were added to a dilute solution of the thioketone (XIV) in benzene, they at once become yellow on the surface and the green colour of the solution faded strongly; the yellow product was collected and shaken with an aqueous solution of potassium iodide in the presence of benzene. The benzene layer was isolated and on evaporation gave unchanged (XIV).

2 : 6-*Bisethylthio*-4-*thio*-3 : 5-*diphenyl*-1-*thiapyrone* (XV).—2 : 6-Bisethylthio-3 : 5-diphenyl-1-thia-γ-pyrone (IV) (Apitzsch, *locc. cit.*) (3 g.) was treated with thionyl chloride (40 c.c.) and thioacetic acid (8 c.c.) as described for (III). The *thioketone* (XV) was obtained after cooling the benzene solution and adding ligroin (b. p. 30—50°); it recrystallised from chloroform in green crystals, m. p. 206° (green melt) (Found: C, 63·0; H, 5·1; S, 32·2. $C_{21}H_{22}S_4$ requires C, 63·0; H, 5·0; S, 32·0%). This thioketone is difficultly soluble in cold ether, and soluble in concentrated sulphuric acid with a yellow colour. When the green solution of the substance in benzene was treated with mercuric chloride crystals, their colour changed immediately to orange and the colour of the solution faded.

Thermal Decomposition of 2 : 6-*Dithio*-3 : 5-*diphenyl*-1-*thia*-γ-*pyranone* (I, R = Ph).—(*a*) The substance (1 g.) was placed in a Pyrex tube through which a stream of dry carbon dioxide was passed for 10 minutes. The tube was then placed in a metal-bath at 120° while the gas was passing, and the temperature of the bath raised to 250° during 6 minutes and kept at 250—260° for 30 minutes. During the experiment white vapours passed over. The contents of the tube when cooled were powdered and washed well with acetone. 2 : 3-6 : 5-*Dithionaphtheno*-1-*thia*-γ-*pyrone* (IX) crystallised from tetralin in light yellow crystals, m. p. 263° (Found: C, 62·65; H, 2·55; S, 29·0. $C_{17}H_8OS_3$ requires C, 62·9; H, 2·5; S, 29·5%). It dissolves with great difficulty in hot benzene, xylene, acetone and chloroform, is soluble in hot nitrobenzene, and dissolves in concentrated sulphuric acid with a yellow colour. When heated at ordinary pressure, it sublimes in long yellow crystals. It is insoluble in cold or hot aqueous alcoholic potash and is not attacked by diazomethane or by boiling with a mixture of acetic acid and concentrated hydrochloric acid (3 : 1).

(*b*) Similar treatment of (I, R = Ph) (2 g.), the temperature being raised to 200° within 2 minutes and kept there for 30 minutes, caused vigorous evolution of hydrogen sulphide, and working up of the solid as in (*a*) afforded (X) or (XII); this crystallised from tetralin and then from nitrobenzene in light yellow crystals, m. p. above 350° [Found: C, 69·1; H, 3·4; S, 21·8. $(C_{17}H_{10}OS_2)_n$ requires C, 69·3; H, 3·4; S, 21·7%]. This *substance* dissolves with great difficulty in the ordinary solvents and gives a yellow colour with concentrated sulphuric acid. It does not react with diazomethane, and is unaffected by 6 hours' refluxing with a mixture of acetic acid and concentrated hydrochloric acid. It (0·5 g.) did not react with sulphur (1 g.) when the mixture was heated in a boiling ethyl phthalate bath for 30 minutes in a stream of carbon dioxide.

(*c*) *Thermal decomposition of* (I, R = Ph) *in nitrobenzene.* The substance was heated under reflux with nitrobenzene (15 c.c.) for 6 hours. The solution when cooled gave light yellow crystals of (X) or (XII) in good yield (Found: C, 69·3; H, 3·64; S, 21·2%).

Action of alcoholic potash on (X) *or* (XII). The substance (0·5 g.) was refluxed with alcoholic potash (3 g. KOH; 50 c.c. alcohol) for ½ hour. The solution was cooled, filtered, and acidified with dilute hydrochloric acid; an orange solid separated on the surface. It was filtered off, dried, crystallised from chloroform, and identified (mixed m. p.) as 2 : 6-dithio-3 : 5-diphenyl-1-thia-γ-pyranone (Apitzsch, *loc. cit.*).

Thermal Decomposition of 2 : 6-*Dithio*-3 : 5-*dimethyl*-1-*thia*-γ-*pyranone* (I, R = CH_3).—(*a*) *Without solvents.* Under conditions similar to those in (*b*) above, this substance decomposed with evolution of hydrogen sulphide, and after 30 minutes at 200—220° the *product* (XI) or (XIII) was worked up as before; it crystallised from tetralin or from benzonitrile in yellowish-white crystals, m. p, above 310° [Found: C, 50·0; H, 3·7; S, 37·8. $(C_7H_6OS_2)_n$ requires C, 49·4; H, 3·5; S, 37·6%]. It is very difficultly soluble in the ordinary organic solvents and dissolves in concentrated sulphuric acid with a yellow colour. It does not react with diazomethane or with acetic and hydrochloric acids as above.

(*b*) *In tetralin.* The substance (1 g.) was dissolved in boiling tetralin (15 c.c.) and refluxed for 4 hours. The solution on cooling gave yellow crystals of (XI) or (XIII) in good yield (Found: C, 49·3; H, 3·8; S, 37·7%).

Action of alcoholic potash on (XI) *or* (XIII). The substance (1 g.) was refluxed with alcoholic potash (alcohol, 40 c.c.; KOH, 2 g.) for 30 minutes. The solution was filtered and acidified with dilute hydrochloric acid, giving an orange semi-solid that solidified on standing. It was filtered off, dried, crystallised from chloroform (m. p. 155°), and identified (mixed m. p.) as (I, R = CH_3) (Apitzsch, *loc. cit.*).

Thermal Rearrangement of 2 : 6-*Bismethylthio*-4-*thio*-3 : 5-*diphenyl*-1-*thia*-γ-*pyrone* (XIV).—0·5 G. was heated in a Monax tube to 240—250° (bath temp.) for 10 minutes. The chloroform solution of the product was evaporated and the residue crystallised from chloroform–light petroleum (b. p. 30—50°). 4 : 6-*Bismethylthio*-2-*thio*-3 : 5-*diphenyl*-1-*thia*-α-*pyrone* (XVI) was obtained in red crystals, m. p. 209° (Found: C, 60·9; H, 4·3; S, 34·7. $C_{18}H_{16}S_4$ requires C, 61·2; H, 4·3; S, 34·4%); it is difficultly soluble in cold ether, insoluble in aqueous potassium hydroxide, and does not react with diazomethane. When mercuric chloride crystals are added to its red solution in benzene, they become orange on the surface. (XVI) (0·5 g.) was recovered unchanged after refluxing for 6 hours with thionyl chloride (15 c.c.). The isomeric change of (XIV) to (XVI) was also effected by dissolving (XIV) in ethyl phthalate and boiling the solution for about 15 minutes.

Thermal Rearrangement of 2 : 6-*Bisethylthio*-4-*thio*-3 : 5-*diphenyl*-1-*thia*-γ-*pyrone* (XV).—0·5 G. was heated in a Monax tube at 220—230° (bath temp.) for 10 minutes. The contents of the tube crystallised from petrol (b. p. 100—150°) in red-brown crystals, m. p. 200° (Found: C, 62·7; H, 5·2; S, 32·2. $C_{21}H_{20}S_4$ requires C, 63·0; H, 5·0; S, 32·0%). 4 : 6-*Bisethylthio*-2-*thio*-3 : 5-*diphenyl*-1-*thia*-α-*pyrone* (XVII) is readily soluble in chloroform and dissolves in concentrated sulphuric acid with a yellowish-brown colour. When mercuric chloride crystals are added to the red benzene solution of (XVII), they acquire an orange-yellow colour. (XVII) (0·5 g.) was recovered unchanged after refluxing for 3 hours with oxalyl chloride (8 g.).

The isomeric change of (XV) to (XVII) can also be effected by dissolving (XV) in ethyl phthalate and boiling the green solution for 10 minutes; after 2 minutes' boiling, the solution becomes red.

Action of Thionyl Chloride or Oxalyl Chloride followed by Water on Thioketones.—2 : 6-*Bisethylthio*-4-*thio*-3 : 5-*diphenyl*-1-*thia*-γ-*pyrone* (XV). 0·5 G. of the pyrone was added to oxalyl chloride (5 g.) (it dissolved immediately, giving a bright red colour) and heated under reflux for 2 hours. The solution was then poured into ice-cold water; the dirty yellow solid which separated was isolated, dried, and crystallised from petrol (b. p. 80—90°); it formed yellowish-white crystals, m. p. 140°, undepressed on admixture with the 1-thia-γ-pyrone (IV) (Apitzsch, *loc. cit.*).

When the bismethylthio-analogue (0·5 g.) was dissolved in thionyl chloride (10 c.c.) (red solution) and refluxed for 4 hours, the excess of thionyl chloride distilled off, and the remaining oil dissolved in benzene (10 c.c.) and shaken with water (20 c.c.), working up of the benzene layer afforded a yellow oil; on being washed with petrol (b. p. 30—50°), this solidified, and crystallisation from petrol (b. p. 90—100°) afforded colourless crystals of (III).

Xanthione, 4-thio-1-thiaflavone (Arndt, Nachtwey, and Pusch, *Ber.*, 1925, **58**, 1644), thiobenzophenone, or 4 : 4′-dimethoxythiobenzophenone (1 g.), similarly treated with thionyl chloride (15 c.c.) for 2 hours, each yielded the corresponding ketone.

3 : 5-*Diphenyl*-1-*thia*-γ-*pyranone* (XVIII).—Apitzsch's preparation (*Ber.*, 1904, **37**, 1609) of (XVIII) was modified as follows. 2 : 6-Dithio-3 : 5-diphenyl-1-thia-γ-pyranone (I, R = Ph) (5 g.) was dissolved in boiling acetic acid (200 c.c.). To this solution, zinc dust (20 g.) was added and then concentrated hydrochloric acid (25 c.c.) in small portions. After ½ hour's boiling, similar additions were made, and the solution was then boiled till the colour became pale yellow (2½ hours in all). The hot solution was filtered, and when cold it was poured into water (250 c.c.). The deposit obtained was collected after 2 hours and separated from alcohol (charcoal) in colourless crystals, m. p. 137° (2 g.).

3 : 5-*Diphenyl*-1-*thia*-γ-*pyrone* (XIX).—The pyranone (XVIII) (1 g.) was dissolved in dry benzene (15 c.c.) and refluxed for 2 hours with phosphorus pentachloride (2 g.); the yellow product which separated was filtered off after cooling, washed with benzene, and then dissolved in alcohol (20 c.c.) (vigorous reaction). The alcoholic solution was poured into ice-cold water (about 200 c.c.) and 3 : 5-*diphenyl*-1-*thia*-γ-*pyrone* (XIX) separated; after 2 hours, it was filtered off and then crystallised from alcohol in light yellow crystals, m. p. 167° (Found: C, 77·4; H, 4·6; S, 12·1. $C_{17}H_{12}OS$ requires C, 77·3; H, 4·5; S, 12·1%).

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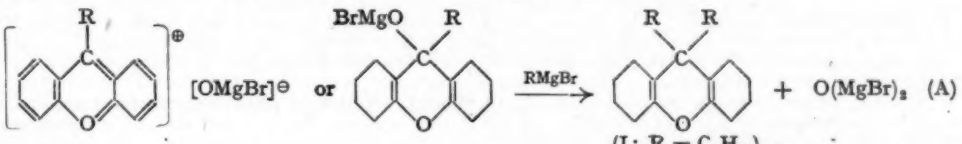
[*Received, November 14th*, 1945.]

124. *Action of Grignard Reagents. Part II.* Replacement of the Oxygen Atoms of Ketones by Two Hydrocarbon Radicals by the Action of Grignard Reagents.*

By Alexander Schönberg and (Miss) Wafia Asker.

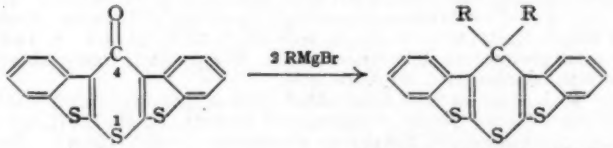
It is shown that xanthone and the 1-thia-γ-pyrone derivative (III) react with Grignard reagents to form not only the carbinols, but also pyranones (see A), the oxygen atoms of the carbonyl groups being replaced by two hydrocarbon radicals; *e.g.*, xanthone yields with phenylmagnesium bromide 9 : 9-diphenylxanthen (I). 2 : 7-Dimethylxanthone (X) is easily obtained by the action of oxalyl chloride on di-*p*-tolyl ether.

Very little is known of the reaction indicated in the title. Ullmann and Engi (*Ber.*, 1904, **37**, 2367) have shown that when xanthone is treated with phenylmagnesium bromide, and the product hydrolysed, phenylxanthhydrol is formed, but a second compound related to xanthen is not recorded. We have found, however, that when the reaction mixture is evaporated to dryness, and then extracted with ligroin, the extract gives colourless 9 : 9-diphenylxanthen (I). A similar reaction was observed with *o*-tolylmagnesium bromide. We ascribe the formation of (I) to the salt-like nature of the primary reaction product.



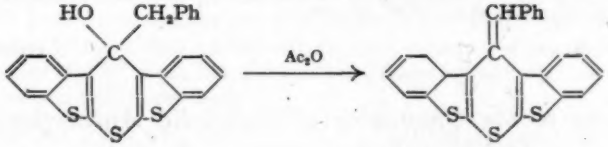
(I; R = C_6H_5.)
(II; R = *o*-C_6H_4Me.)

In the above cases the carbinol, *e.g.*, phenylxanthhydrol, was the main product under our experimental conditions, and the second product, *e.g.*, (I), was obtained only in small yield; but when phenylmagnesium bromide or *m*-tolylmagnesium bromide was allowed to react on 2 : 3·6 : 5-dithionaphtheno-1-thia-γ-pyrone (III), 4 : 4-*diphenyl-* (V) and 4 : 4-*di*-m-*tolyl*-2 : 3-6 : 5-*dithionaphtheno*-1-*thia*-γ-*pyran* (VI) were obtained in good yield; in these two cases, the reaction mentioned in the title predominates. When (III) was treated



(III.) (IV, R = CH_2Ph.) (V, R = Ph.)
(VI, R = *m*-C_6H_4Me.)

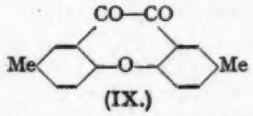
with benzylmagnesium chloride followed by hydrolysis, 4 : 4-*dibenzyl-* (IV) and 4-*hydroxy*-4-*benzyl*-2 : 3-6 : 5-*dithionaphtheno*-1-*thia*-γ-*pyran* (VII) were obtained, the former when a comparatively large amount of



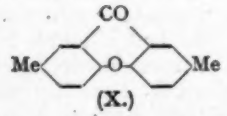
(VII.) (VIII.)

benzylmagnesium chloride was used. The latter on treatment with acetic anhydride yielded the 4-*benzylidene* compound (VIII).

An Easy Method for Preparation of 2 : 7-*Dimethylxanthone* (X).—Schönberg and Aly Sina devised the following method. Oxalyl chloride was allowed to act on di-*p*-tolyl ether in the presence of aluminium chloride in the hope that (IX) might be synthesised. However, 2 : 7-dimethylxanthone (X) was obtained in a good yield. This reaction may be explained by the formation of carbonyl chloride by the action of aluminium chloride on oxalyl chloride (cf., *inter alia*, Staudinger, *Ber.*, 1908, **41**, 3561).



(IX.)



(X.)

Experimental.

9 : 9-*Diphenylxanthen* (I).—To an ethereal solution of phenylmagnesium bromide [prepared from magnesium (1·5 g.), bromobenzene (15 g.), and ether (40 c.c.)], xanthone (5 g.) and dry benzene (30 c.c.) were added. The mixture was refluxed for 5 hours and set aside overnight. The solvents were then distilled off on a water-bath, and the residue

* Schönberg and Moubasher (*J.*, 1944, 462) is regarded as Part I.

extracted several times with petrol (b. p. 50—60°). The extract was evaporated, and the residue steam distilled (to remove diphenyl). The residue crystallised from acetic acid in almost colourless crystals (0·5 g.), m. p. 199° undepressed on admixture with an authentic specimen (Ullmann and Engi, *loc. cit.*) (Found: C, 89·4; H, 5·4. Calc. for $C_{25}H_{18}O$: C, 89·8; H, 5·4%).

9 : 9-*Di-o-tolylxanthen* (II).—By an exactly analogous procedure *o*-tolylmagnesium bromide and xanthone gave colourless crystals which, recrystallised from alcohol, had m. p. 119° (Found: C, 90·1; H, 5·9. $C_{27}H_{22}O$ requires C, 90·0; H, 6·1%).

Action of Benzylmagnesium Chloride on 2 : 3-6 : 5-*Dithionaphtheno*-1-*thia*-γ-*pyrone* (III).—(*a*) The pyrone (III) (see preceding paper) (1 g.) was treated with an ethereal solution of benzylmagnesium chloride, prepared from benzyl chloride (5·5 g.), magnesium (0·8 g.), and ether (30 c.c.), in the presence of dry benzene (20 c.c.) and refluxed for 5 hours. The yellow oil obtained after decomposition of the product with cold dilute hydrochloric acid was washed with ligroin (b. p. 30—50°) and then crystallised from ligroin (b. p. 100—110°) in almost colourless crystals, m. p. 176° (Found: C, 75·7; H, 4·83; S, 20·1. $C_{31}H_{22}S_3$ requires, C, 75·9; H, 4·5; S, 19·6%). 4 : 4-*Dibenzyl*-2 : 3-6 : 5-*dithionaphtheno*-1-*thia*-γ-*pyran* (IV) dissolves in concentrated sulphuric acid with a yellow colour; it (0·3 g.) was recovered unchanged after refluxing for 3 hours with acetic anhydride (20 c.c.).

(*b*) The pyrone (2 g.) was treated similarly with the same amount of benzylmagnesium chloride as above. The yellowish-brown oil ultimately obtained was washed several times with ligroin (b. p. 30—50°), and 4-*hydroxy*-4-*benzyl*-2 : 3-6 : 5-*dithionaphtheno*-1-*thia*-γ-*pyran* (VII) then crystallised from xylene after the addition of ligroin (b. p. 30—50°) in light yellow crystals, m. p. 220° (Found: C, 69·2; H, 3·55; S, 22·4. $C_{24}H_{16}OS_3$ requires C, 69·2; H, 3·8; S, 23·0%).

Action of acetic anhydride on (VII). The pyran (0·5 g.) was dissolved in acetic anhydride (20 c.c.), the solution refluxed for 3 hours, concentrated, and cooled, affording light yellow crystals, m. p. 244° (Found: C, 72·3; H, 3·7; S, 24·4. $C_{24}H_{14}S_3$ requires C, 72·4; H, 3·5; S, 24·1%), of 4-*benzylidene*-2 : 3-6 : 5-*dithionaphtheno*-1-*thia*-γ-*pyran* (VIII), difficultly soluble in hot benzene.

Action of Arylmagnesium Bromides on (III).—(*a*) To an ethereal solution of phenylmagnesium bromide [from magnesium (0·9 g.), bromobenzene (9 g.), and dry ether (25 c.c.)], dry benzene (50 c.c.) and (III) (1 g.) were added. The mixture was refluxed, with stirring, for 5 hours, the ether being allowed to evaporate slowly. The substance dissolved completely to give an orange-yellow solution. The reaction mixture was kept overnight and then decomposed with cold water followed by dilute hydrochloric acid. The organic matter was extracted with ether, and the oil remaining after evaporation of the ether was washed with ligroin (b. p. 30—50°). The residue crystallised from ligroin (b. p. 100—110°) in yellow crystals, m. p. 235° (Found: C, 75·5; H, 4·1; S, 20·3. $C_{29}H_{18}S_3$ requires C, 75·4; H, 3·9; S, 20·7%). 4 : 4-*Diphenyl*-2 : 3-6 : 5-*dithionaphtheno*-1-*thia*-γ-*pyran* (V) is freely soluble in benzene, gives no colour reaction with concentrated sulphuric acid, and contains no active hydrogen.

(*b*) 1 G. of (III) was treated with *m*-tolylmagnesium bromide (prepared from 9 g. of *m*-bromotoluene) as described above. The yellowish-brown oil obtained was washed with ligroin (b. p. 30—50°) and then with boiling alcohol. The remaining yellow solid was powdered and then crystallised from ligroin (b. p. 100—110°); after cooling and scratching, yellow crystals of 4 : 4-*di*-m-*tolyl*-2 : 3-6 : 5-*dithionaphtheno*-1-*thia*-γ-*pyran* (VI) were obtained, m. p. 219° [Found: C, 75·9; H, 4·62; S, 19·6; *M* (micro-Rast), 488. $C_{31}H_{22}S_3$ requires C, 75·9; H, 4·5; S, 19·6%; *M*, 490]. The ligroin and the alcohol washings gave more product on slow evaporation. The pyran is freely soluble in benzene but difficultly in alcohol, and gives no colour with concentrated sulphuric acid.

2 : 7-*Dimethylxanthone* (X).—In a three-necked flask fitted with a mercury-sealed mechanical stirrer and a condenser, finely divided di-*p*-tolyl ether (10 g.) (Reilly, Drumm, and Barrett, *J.*, 1927, 67) was mixed with oxalyl chloride (25 g.), carbon disulphide (75 c.c.), and powdered anhydrous aluminium chloride (10 g.). The mixture was stirred first under ice-cooling for 2 hours, then after the addition of further 8 g. of aluminium chloride for another 4 hours, and finally left overnight. The solution was then acidified with dilute hydrochloric acid, the organic layer separated, and the carbon disulphide driven off on a water-bath. The residue was powdered, digested with hot 10% sodium carbonate solution until free acid was removed, washed with distilled water until free from sodium carbonate, dried on the pump, and then crystallised from alcohol. The 2 : 7-dimethylxanthone (X) had m. p. 143°; yield 80% (Found: C, 80·4; H, 5·54. Calc. for $C_{15}H_{12}O_2$: C, 80·4; H, 5·4%). For identification it was converted into 2 : 7 : 2′ : 7′-tetramethyldixanthylen (Gurgenjanz and Kostanecki, *Ber.*, 1895, **28**, 2311).

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125. *Contributions to the Chemistry of Synthetic Antimalarials. Part II. Tetrahydropamaquin.**

By H. J. BARBER and W. R. WRAGG.

The synthesis of 8-(4′-*diethylamino*-1′-*methylbutyl*)*amino*-6-*methoxy*-1 : 2 : 3 : 4-*tetrahydroquinoline*, hereinafter referred to as tetrahydropamaquin, and of some allied compounds, is described. Tetrahydropamaquin appears to be better absorbed and about four times less toxic than pamaquin, while possessing a comparable schizonticidal activity against *P. gallinaceum* and *P. lophuræ*.

No attempts at systematic modification of the quinoline nucleus of the pamaquin molecule have been recorded, and in this and the following paper the aim has been to confine the modification to a single simple step at a time, to determine how far the heterocyclic ring could be altered without loss of activity.

Tetrahydropamaquin thus had a double interest. First, it was a possible trace impurity in commercial pamaquin (prepared by a synthesis involving catalytic reductions) and clearly a knowledge of its toxicity and activity was of some importance. Secondly, the reduction of the quinoline nucleus to the tetrahydro derivative would convert the pyridine ring into one of aliphatic character, without appreciably altering the structure or complexity of the entire molecule.

Few tetrahydroquinolines have figured in the chemotherapy of malaria and even the parent substance,

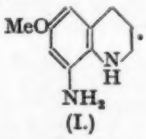
* Much of the work described here forms the subject of B.P. Application 3340/43. Since this paper was submitted, (I) above has been described, together with its picrate and iminazole derivatives, in a note by Price and Herbrandson (*J. Amer. Chem. Soc.*, 1946, **68**, 910).

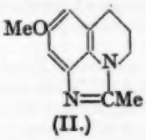
8-amino-6-methoxy-1 : 2 : 3 : 4-tetrahydroquinoline (I), had not hitherto been described. Two routes to tetrahydropamaquin were possible; direct reduction of pamaquin, or the introduction of the side chain into the parent tetrahydroquinoline. The latter method was preferred in the first place. The separation of tetrahydropamaquin from any unreduced pamaquin would not have been expedient since bases of this type are all high-boiling viscous liquids not characterised by crystalline salts. Moreover, many of the normal methods of reducing quinolines to tetrahydroquinolines would remove the side chain. All the tetrahydroquinolines described were preserved in an oxygen-free atmosphere, as they discoloured rapidly in contact with air.

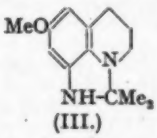
The catalytic reduction of 8-nitro-6-methoxyquinoline was studied in detail, since the presence of the tetrahydro-compound as an impurity in technical 8-amino-6-methoxyquinoline concerned the first object of this work. Most previous workers recorded melting points for 8-amino-6-methoxyquinoline between 41° and 42°, except Tschitschibabin and Hoffmann (*Compt. rend.*, 1939, **208**, 525), who gave 52°. Reduction with ammonium sulphide (or its equivalent), iron and acid, and stannous chloride has commonly been used in the preparation of this intermediate. Catalytic reduction in acetic acid solution was employed by Rothmann (D.R-P. 567,923, 1931), and recently Crum and Robinson (*J.*, 1943, 561), using Raney nickel catalyst in methanol, obtained a product, m. p. 41°. Further, Mosher (Pennsylvania State College, Ph.D. Thesis, 1942) reported that catalytic reduction of the corresponding 6-ethoxy-compound using Raney nickel was unsatisfactory, yielding a mixture of products. Our preliminary catalytic reductions of 8-nitro-6-methoxyquinoline in ethyl acetate with Raney nickel gave products which rapidly discoloured and partly decomposed on distillation. This was traced to over-reduction, and the readily oxidisable tetrahydroquinoline (I) was isolated (<1% when the reduction temperature remained <75°). The optimum reduction temperature was found to be 60—65°.

Crystallisation of the slightly water-soluble hydrochloride of 8-amino-6-methoxyquinoline (cf. Tschitschibabin and Hoffmann, *loc. cit.*) separated this base from the more soluble hydrochloride of the unstable tetrahydro-base. The regenerated base then proved quite stable in air, was almost white, and had m. p. 50—51°.

When the preparation of (I) by catalytic reduction of 8-amino-6-methoxyquinoline was attempted it was found that reaction with the solvent, ethyl acetate, in the presence of Raney nickel at 110°/40 atmospheres led to the formation (40% yield) of *5-methoxy-2-methyl-1 : 7-trimethylenebenziminazole* (II), together with the required product (I). This was attributed to the catalytic effect of an impurity in the ethyl acetate since under


(I.)


(II.)


(III.)

apparently identical conditions, but with different batches of materials, smooth reduction to (I) alone resulted. Contamination of (I) by side reaction with the solvent was eliminated when dioxan was substituted. The iminazole (II) was prepared directly from (I), the latter being further characterised as its *dibenzoyl* derivative. Acetone condensed with (I) to form a well-defined but somewhat unstable *anhydro*-compound (III).

The 5-diethylaminopentan-2-one used in this work was purified *via* its diethyl acetal. 5-Diethylamino-2 : 2-diethoxypentane (IV) was prepared from the purified ketone in 95% yield compared with the 60% yield obtained with crude ketone. This acetal underwent thermal decomposition in the presence of ammonium chloride at temperatures above 140° with the elimination of one molecule of alcohol from each molecule of acetal, leaving *5-diethylamino-2-ethoxypent-2-ene* (V).

$CH_3 \cdot C(OEt) : CH \cdot CH_2 \cdot CH_2 \cdot NEt_2$ (V.)

$CH_2 : C(OEt) \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NEt_2$ (VI.)

Ozonolysis gave no formaldehyde, thus excluding a terminal methylene group as in (VI).

The acetal (IV) condensed in the presence of ammonium chloride with the tetrahydroquinoline (I) to form the *anil* (VII). The monoethoxy base (V) condensed similarly and the product, on reduction, yielded *tetrahydropamaquin*. Hydrogenation of the anil (VII) failed in the presence of Raney nickel and platinum on charcoal catalysts. Sodium in ethyl alcohol produced only incomplete reduction, but a 60% yield of tetrahydropamaquin was realised with sodium in amyl alcohol. Tetrahydropamaquin has also been prepared directly from pamaquin by the catalytic method and by means of sodium in amyl alcohol, the product being identified by refractive index, analysis, and boiling point.

It was found that pamaquin was not acetylated by treatment with acetic anhydride in pyridine. Under these conditions, therefore, the 1 position of tetrahydropamaquin alone should have acetylated. However, the reaction product proved complex, the iminazole (II) being isolated as picrate in 10% yield together with an unidentified demethylated compound of totally unexpected properties in *ca.* 10% yield.

Dr. A. O. Seeler, of the Merck Institute for Therapeutic Research, Rahway, N.J., U.S.A., has kindly furnished the following biological data obtained from his initial examination of our product:

" The activity of the isethionate of tetrahydropamaquin was compared with that of the isethionate of pamaquin against certain avian malaria infections. Both drugs were administered as aqueous solutions into the crops of the birds once daily. Tetrahydropamaquin was found to be approximately two and a half times as active as pamaquin against the schizonts of *Plasmodium gallinaceum* in chicks and about equally as active as

pamaquin against the schizonts of *P. lophuræ* in ducklings. Both tetrahydropamaquin and pamaquin prolonged the incubation period of sporozoite induced *P. gallinaceum* infections when administered at the highest tolerated dose levels for three days after the inoculation of the chicks.

" Determinations of the blood concentrations in groups of rats three hours after the oral administration of 10 mg. per kg. of tetrahydropamaquin and of 10 mg. per kg. of pamaquin, gave average blood values of 260 micrograms per l. of tetrahydropamaquin and 100 micrograms per l. of pamaquin. Neither drug could be detected in the blood twenty-four hours after a single oral dose of 10 mg. per kg.

" The $L.D._{50}$ of tetrahydropamaquin after four weeks of administration to 200 gram albino rats was found to be 30 mg. per kg. while the $L.D._{50}$ of pamaquin in the same experiment was found to be about 7·5 mg. per kg.

" Two *Macacus Rhesus* monkeys were given 10 mg. per kg. of tetrahydropamaquin by stomach tube once daily for two weeks. Neither monkey showed any evidence of distress and there was no weight loss. Gross examination of the organs on autopsy revealed no evidence of pathological changes. One of the two monkeys developed a slight normocytic anæmia during the experiment. Methæmoglobin could not be detected in either monkey."

A full account of the results of subsequent biological examination in the Biological Laboratories, May & Baker Ltd., will be published elsewhere. This work suggests a somewhat modified conclusion in that the decreased toxicity of tetrahydropamaquin appears to be offset by a corresponding decrease in antimalarial activity. Tests in our own laboratories have shown that the iminazole (II) is devoid of activity against *P. gallinaceum* in chicks when administered subcutaneously.

Experimental.

8-Amino-6-methoxyquinoline.—8-Nitro-6-methoxyquinoline (150 g.) was hydrogenated in ethyl acetate (750 c.c.) at 60—65°/20 atmospheres in the presence of Raney nickel catalyst (10 g.), until a definite break in the hydrogen absorption curve was observed. The residual oil, after removal of solvent, was converted into hydrochloride and crystallised from hot water. The hydrochloride was washed free of mother liquors with cold 2N-hydrochloric acid until the washings did not deepen in colour on addition of a few drops of ferric chloride solution—a test for over-reduced product. A second crystallisation was sometimes necessary. The pure hydrochloride was dissolved in the minimum amount of water and basified with 50% sodium hydroxide. The solid base was collected, washed free of alkali, dried, and distilled as a bright yellow oil b. p. 170°/4 mm., which recrystallised in rhombs, m. p. 50—51° (102 g., 80% yield). The bright red crystalline *monoisethionate*, obtained by treating 8-amino-6-methoxyquinoline dissolved in alcohol with concentrated isethionic acid, crystallised from alcohol as rectangular rods, m. p. 153—154° (corr.), soluble in water (Found : N, 9·05. $C_{10}H_{10}ON_2,C_2H_6O_4S$ requires N, 9·3%).

Catalytic Reduction of 8-Amino-6-methoxyquinoline.—(a) *Ethyl acetate as solvent.* 8-Amino-6-methoxyquinoline (100 g.) was hydrogenated in ethyl acetate (385 c.c.) at 110°/40 atmospheres in the presence of 25% Raney nickel. After 17 hours the absorption of hydrogen ceased. Two fractions were obtained on distillation in a hydrogen atmosphere. One, b. p. 175—185°/1 mm., a yellow oil (50 g.), proved to be the required product, *8-amino-6-methoxy-1 : 2 : 3 : 4-tetrahydroquinoline* (I) (Found : C, 67·3; H, 7·87. $C_{10}H_{14}ON_2$ requires C, 67·4; H, 7·86%). The fraction, b. p. 195—200°/1 mm., crystallised to a yellow solid (25 g.), m. p. 113—116°. Purification raised this to 120—121° (corr.), mixed m. p. 120—121° (corr.) with authentic iminazole (II). The base was confirmed to be identical with (II) by preparation of the picrate, m. p. 252—254° (corr.).

Authentic iminazole (II) was prepared from the tetrahydroquinoline (I) (20 g.) by refluxing with glacial acetic acid (20 c.c.), acetic anhydride (20 c.c.), and a few drops of concentrated sulphuric acid for 10 hours in hydrogen. *5-Methoxy-2-methyl-1 : 7-trimethylenebenziminazole* (II), liberated by excess ammonia, was extracted with chloroform, and crystallised twice from hot water (2 l.) as fluffy colourless needles (15 g.), m. p. 120—121° (corr.) (Found : C, 71·1; H, 7·15; N, 14·1. $C_{12}H_{14}ON_2$ requires C, 71·3; H, 6·93; N, 13·9%). The *picrate* crystallised from acetone in long golden needles, m. p. 253—254° (corr.) (Found : N, 16·4. $C_{12}H_{14}ON_2,C_6H_3O_7N_3$ requires N, 16·2%).

(b) Subsequent reductions as (a) above gave no iminazole on careful fractionation. The high-boiling fractions were proved to be the tetrahydroquinoline (I) by conversion in good yield to *picrate* as brown needles from alcohol, m. p. 163—164° (corr., decomp.) (Found on picrate dried over sulphuric acid at 25°/10 mm. : N, 16·5. $C_{10}H_{14}ON_2,C_6H_3O_7N_3,H_2O$ requires N, 16·5%. Found on picrate dried at 80°/10 mm. : N, 17·2. $C_{10}H_{14}ON_2,C_6H_3O_7N_3$ requires N, 17·2%). The picrate in acetone solution rapidly developed a dark green colour and decomposed on warming, whereas it could be readily crystallised from alcohol.

(c) *Dioxan as solvent.* 8-Amino-6-methoxyquinoline (106 g.) was hydrogenated in dioxan (300 c.c.) at 110—135°/40 atmospheres in the presence of 24% Raney nickel catalyst. An uptake of 110% of the theoretical for 4H was observed. The tetrahydroquinoline (I) was obtained as a bright yellow oil (87 g.), b. p. 190°/3 mm. It slowly crystallised in thick plates, m. p. 43—45° (Found : C, 67·9; H, 7·7; N, 15·7. Calc. for $C_{10}H_{14}ON_2$: C, 67·4; H, 7·86; N, 15·7%). The base was converted into the picrate, m. p. 163—164°. The *hydrochloride*, prepared by precipitation of an aqueous solution with acetone, crystallised from dry methanol–ether as thick colourless rhombs, m. p. 211—212°, which slowly became red in air (Found : C, 55·6; H, 6·99; Cl, 16·5. $C_{10}H_{14}ON_2,HCl$ requires C, 56·0; H, 7·04; Cl, 16·55%).

The tetrahydroquinoline (I) was treated with benzoyl chloride (2·2 mol.) in pyridine; the *dibenzoyl* derivative, isolated in the usual manner, crystallised from aqueous acetone as colourless elongated rhombic prisms, m. p. 205—206° (corr.) (Found : C, 74·5; H, 5·55; N, 7·4. $C_{24}H_{22}O_3N_2$ requires C, 74·6; H, 5·73; N, 7·25%).

The tetrahydroquinoline (I) (8 g.) was warmed with acetone (18 c.c.) in a nitrogen atmosphere. After 24 hours the red liquor was decanted from a crop of large reddish needles (3 g.) which were then washed free of red contamination with very small portions of acetone. They crystallised from light petroleum (b. p. 80—100°) as small colourless needles, m. p. 119° (corr.), which became red in air (Found : C, 71·6; H, 8·25; N, 12·9; OMe, 14·3. $C_{13}H_{18}N_2(OMe)$ requires C, 71·55; H, 8·25; N, 12·8; OMe, 14·25%). The compound was therefore the anhydro-condensation *product*. The formulation 5-methoxy-2 : 2-dimethyl-1 : 7-trimethylene-2 : 3-dihydrobenziminazole (III) was preferred because catalytic reduction in ethyl acetate in the presence of Adams's catalyst at 20°/1 atmosphere failed, indicating that the substance was probably not the *iso*propylidene derivative. However, hydrolysis of the product not only occurred when it was treated with cold hydrochloric acid but also when its solution in 98% alcohol was treated with alcoholic picric acid, which precipitated the picrate of the tetrahydroquinoline (I).

5-Diethylamino-2-ethoxypent-2-ene (V).—Redistilled 5-diethylamino-2 : 2-diethoxypentane, b. p. 121—122°/22 mm. (200 c.c.), was vigorously stirred with ammonium chloride (5 g.) in a flask fitted with a short column. When the internal

temperature was raised to 140°, alcohol began to distil. The temperature was maintained at 200° for 2 hours. After 1 hour, a further quantity of ammonium chloride (5 g.) was added to ensure a complete reaction. Practically the theoretical volume of alcohol was collected. The evil-smelling residue was distilled and the fraction, b. p. 86°/13 mm. (75% yield), proved to be the unsaturated monoethoxy *base* (V) (Found: OEt, 24·5. $C_9H_{18}N(OEt)$ requires OEt, 24·4%). Hydrogenation of a 20% solution in ethanol in the presence of 8% Raney nickel at 60°/30 atmospheres resulted in 95% of the theoretical uptake for one double bond.

The monoethoxy base (V) (0·925 g.) in carbon tetrachloride (10 c.c.) was ozonolysed at −10°. No formaldehyde could be detected as its 2 : 4-dinitrophenylhydrazone.

Tetrahydropamaquin.—(a) *Condensation with 5-diethylamino-2 : 2-diethoxypentane.* 8-Amino-6-methoxy-1 : 2 : 3 : 4-tetrahydroquinoline (52 g.) was vigorously stirred with 5-diethylamino-2 : 2-diethoxypentane (79 g.) and ammonium chloride (0·4 g.) in a slow stream of hydrogen. The internal temperature was raised from 145° to 160° during one hour and from 160° to 190° during the second hour; 31 c.c. (theory, 36·5 c.c.) of alcohol distilled. Sodium bicarbonate (0·5 g.) was added to the dark yellow reaction mixture and stirring continued for 10 minutes. Ethyl acetate (350 c.c.) was added, but attempted hydrogenation of the crude anil in the presence of platinum on charcoal catalyst at 60°/32 atmospheres failed. The anil was recovered and the fraction, b. p. 180—190°/0·1 mm. (65 g.), 8-(4′-*diethylamino*-1′-*methylbutylidene*)*amino*-6-*methoxy*-1 : 2 : 3 : 4-*tetrahydroquinoline* (VII) collected (Found: C, 71·6; H, 9·8. $C_{19}H_{31}ON_3$ requires C, 71·9; H, 9·8%). Attempted reduction of this base in ethyl acetate (300 c.c.) at 60°/32 atmospheres, using 6% platinum on charcoal catalyst or 9% Raney nickel, failed.

The recovered anil was poured quickly into anhydrous amyl alcohol (1600 c.c.) at 80° to which sodium (90 g.) had just previously been added. As much of the sodium as possible was dissolved by refluxing the alcohol; the residue was dissolved by addition of methanol. An atmosphere of hydrogen was maintained over the reaction mixture during the following operations. Unchanged anil was hydrolysed by warming on the steam-bath with excess of hydrochloric acid. The amyl alcohol was removed by rapid steam distillation, after neutralisation (litmus). The residual liquors were acidified (Congo red) and ether-extracted, and then basified strongly with 50% sodium hydroxide before exhaustive ether extraction. The latter extract was dried over potassium carbonate and carefully fractionated, using an electrically heated Vigreux column, to yield 8-(4′-*diethylamino*-1′-*methylbutyl*)*amino*-6-*methoxy*-1 : 2 : 3 : 4-*tetrahydroquinoline* (*tetrahydropamaquin*) (33 g.), b. p. 175—180°/0·05 mm., $n_D^{25°}$ 1·5435 (Found: C, 71·5; H, 10·1; N, 13·1. $C_{19}H_{33}ON_3$ requires C, 71·5; H, 10·35; N, 13·2%). Tetrahydropamaquin was stored under carbon dioxide.

(b) *Condensation with unsaturated monoethoxy base* (V). The preparation of tetrahydropamaquin, using this compound instead of the acetal, gave a product identical with that above (40% yield) (Found: OMe, 9·7. $C_{18}H_{30}N_3(OMe)$ requires OMe, 9·7%).

(c) *Reduction of pamaquin base.* 8-(4′-Diethylamino-1′-methylbutyl)amino-6-methoxyquinoline (36 g.) was reduced in anhydrous amyl alcohol (1300 c.c.) with sodium (100 g.), by the method described above for the reduction of the anil (VII). Tetrahydropamaquin (27·5 g.), b. p. 175—180°/0·05 mm., $n_D^{25°}$ 1·5445, was obtained (Found: C, 71·5; H, 10·0. Calc. for $C_{19}H_{33}ON_3$: C, 71·5; H, 10·35%).

8-(4′-Diethylamino-1′-methylbutyl)amino-6-methoxyquinoline (99 g.) was hydrogenated in dioxan (200 c.c.) in the presence of 20% Raney nickel catalyst at 120°/30 atmospheres until no further absorption of hydrogen took place. The crude base was dissolved in 2N-hydrochloric acid and ether-extracted. The acid liquor was basified and ether-extracted. Distillation of this extract yielded tetrahydropamaquin (85 g.), b. p. 175—180°/0·05 mm., $n_D^{20°}$ 1·5440.

Tetrahydropamaquin (15·5 g.) was converted into the hydrochloride in water (1 l.) saturated with carbon dioxide, made slightly acid (Congo red), and run with vigorous stirring, under an atmosphere of carbon dioxide, into a slightly alkaline (phenolphthalein) solution of 2 : 2′-dihydroxy-1 : 1′-dinaphthylmethane-3 : 3′-dicarboxylic acid (18·8 g.) in aqueous ammonia (3000 c.c.) containing sodium bisulphite (5 g.). The cream *salt* (31 g.) was collected, washed with air-free water containing a trace of sulphur dioxide, and dried (P_2O_5) (Found: N, 5·35. $C_{19}H_{33}ON_3.C_{22}H_{16}O_6$ requires N, 5·95%).

Acetylation of Tetrahydropamaquin.—Tetrahydropamaquin (10 g.) dissolved in dry pyridine (10 c.c.) was treated with acetic anhydride (3·5 c.c.). Next day it was heated on the steam-bath for 2 hours. The low-boiling material was removed at 0·01 mm. (up to 100°). The residue, in benzene (200 c.c.), was washed first with 2N-sodium hydroxide (50 c.c.) and then with water (25 c.c., 50 c.c.). The benzene layer was dried (Na_2SO_4) and evaporated. The residue distilled as a thick yellow oil (3 g.), b. p. 195°/0·05 mm., which was probably impure acetylated tetrahydropamaquin, and gave a picrate soluble in acetone.

The alkaline aqueous layer was neutralised, the water removed at room temperature, and the residue extracted with dry alcohol. The alcohol left a residue which distilled as a yellow oil mixed with a brown solid (4·8 g.). This mixture was dissolved in acetone (15 c.c.); light petroleum (15 c.c.) precipitated a white solid (0·9 g.) which was crystallised repeatedly from alcohol and obtained as small, colourless, irregular flat needles, m. p. 260—300° (slow decomp.) (Found: C, 58·8; H, 5·9; N, 12·2%. Repeat preparation, found: C, 58·6; H, 6·1; N, 12·25; OMe, <0·1%. The compound proved insoluble in camphor). The acetone–light petroleum liquors yielded a picrate (1·4 g.) which was recrystallised from a large volume of acetone, m. p. 249—251° (corr.). Mixed m. p. with authentic 5-methoxy-2-methyl-1 : 7-trimethylenebenziminazole picrate, 249—251° (corr.). From a separate experiment the iminazole was isolated, m. p. 115—116° (corr.). Mixed m. p. with authentic base, 115—119° (corr.) (Found: N, 13·6; OMe, 15·5. Calc. for $C_{11}H_{11}N_2(OMe)$: N, 13·88; OMe, 15·35%).

Grateful acknowledgment is made to Mr. S. Bance, B.Sc., A.R.I.C., for the semi-microanalyses; to Dr. A. O. Seeler at the Merck Institute for Therapeutic Research and to the Biological Division, May & Baker Ltd., for the biological results; and to the Directors of Messrs. May & Baker Ltd. for permission to publish these results.

RESEARCH LABORATORIES, MESSRS. MAY & BAKER LTD.,
DAGENHAM, ESSEX.

[*Received, October 24th*, 1945.]

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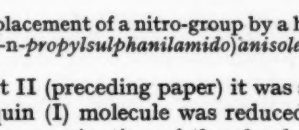
126. *Contributions to the Chemistry of Synthetic Antimalarials. Part III. An Open Ring Analogue of Tetrahydropamaquin.*

By H. J. BARBER, F. W. MAJOR, and W. R. WRAGG.

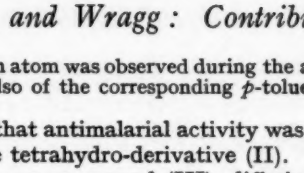
4-n-*Propylamino*-3-(4′-*diethylamino*-1′-*methylbutyl*)*aminoanisole*, a compound of strong structural similarity to tetrahydropamaquin [8-(4′-diethylamino-1′-methylbutyl)amino-6-methoxy-1 : 2 : 3 : 4-tetrahydroquinoline], has been prepared, and its hydrochloride shown to have only slight antimalarial activity against *P. gallinaceum* and to be ineffective against *P. relictum*. An interesting reaction involving the

replacement of a nitro-group by a hydrogen atom was observed during the acid hydrolysis of 3-*nitro*-4-(N⁴-*acetyl*-N¹-n-*propylsulphanilamido*)*anisole*, and also of the corresponding *p*-toluenesulphonamide.

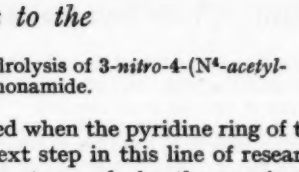
In Part II (preceding paper) it was shown that antimalarial activity was retained when the pyridine ring of the pamaquin (I) molecule was reduced to the tetrahydro-derivative (II). The next step in this line of research was the examination of the closely analogous compound (III), differing in structure only by the opening of the reduced pyridine ring.



(I.)



(II.)

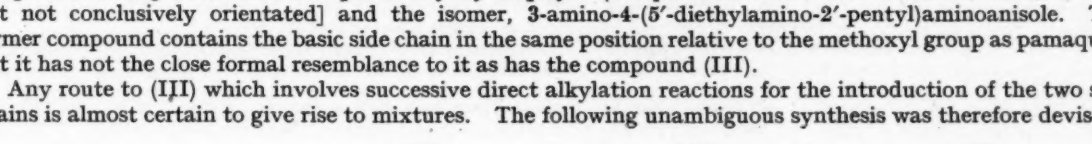


(III.)

This modification resulted in almost entire loss of antimalarial activity. Only three other active benzenoid derivatives appear to have been described in the literature (Fourneau *et al.*, *Ann. Inst. Pasteur*, 1930, **44**, 503); one of these showed definite activity in canaries, but was without effect in man.

Two compounds similar to our product have been described. Simonov (*J. Gen. Chem. Russia*, 1940, **10**, 1588) reported the preparation of 3-amino-4-(3′-diethylaminopropyl)aminoanisole by a route similar to that described here for 3-*amino*-4-n-*propylaminoanisole* (VI). Since this work was first completed Clemo and Swan (*J.*, 1944, 274) have described 4-amino-3-(5′-diethylamino-2′-pentyl)aminoanisole [the corresponding 4-nitro-compound having been described previously by Topeijev (*Compt. rend. Acad. Sci. U.R.S.S.*, 1935, **4**, 201) but not conclusively orientated] and the isomer, 3-amino-4-(5′-diethylamino-2′-pentyl)aminoanisole. The former compound contains the basic side chain in the same position relative to the methoxyl group as pamaquin, but it has not the close formal resemblance to it as has the compound (III).

Any route to (III) which involves successive direct alkylation reactions for the introduction of the two side chains is almost certain to give rise to mixtures. The following unambiguous synthesis was therefore devised:



(IV.) (V.) (VI.) (VII.)

3-Nitro-4-aminoanisole was converted into a *sulphonamide* (IV). It was found preferable to use the 4-N⁴-acetylsulphanilamide rather than the 4-*p*-toluenesulphonamide, as on acid hydrolysis the former rapidly yields the sulphanilyl derivative which, being soluble in acid, is more readily hydrolysed to the free amine. The sulphonamide (IV) by alkylation with propyl bromide followed by drastic acid hydrolysis, gave the *nitroamine* (V). This hydrolysis was not uncomplicated, since partial elimination of the nitro-group occurred, and about 12% of 4-n-*propylaminoanisole* (VIII) was isolated.

The mechanism of this side reaction is being more fully examined, but some of its features are recorded here. Replacement of the nitro group by a hydrogen atom took place to almost precisely the same extent during the hydrolysis of both 3-*nitro*-4-(N⁴-*acetyl*-N¹-n-*propylsulphanilamido*)*anisole* (IX) and the corresponding p-*toluenesulphonamide* derivative (X). No low-boiling fraction corresponding to (VIII) could be detected when the sulphonamide (IV; R = C_6H_4·NHAc) was hydrolysed under identical conditions. During hydrolysis of the sulphonamide (X) brown gases were evolved, and in one experiment an attempt was made to absorb them in dilute alkali. Analysis of the alkali yielded values for total nitrogen and nitrite which agreed exactly, but which accounted for only 20% of the theoretical quantity of nitrogen, calculated on the basis of the 4-*n*-propylaminoanisole actually isolated. The fact that nitrate was absent was unexpected, but sufficient evidence has accrued to confirm that the nitro-group was indeed eliminated, although the nature of the reaction is at present obscure. It may be noted that it is the 3-nitro-group of 3 : 4-dinitroanisole which reacts with amines (Topeijev, *loc. cit.*), although here the predominant influence is probably the adjacent nitro-group in the 4-position. No oxides of nitrogen could be detected during the hydrolysis of the sulphonamide (IX), but this was not unexpected as sulphanilic acid was simultaneously formed in the acid hydrolysis mixture.

The unexpected physical properties of the nitroamine (V) prompted the alternative preparation of this intermediate by a less convenient method, *viz.*, the action of propylamine on 4-bromo-3-nitroanisole, to confirm its identity. Reduction of (V) gave the diamine (VI), a very readily oxidised base, which on condensation with 5-diethylamino-2 : 2-diethoxypentane yielded the anil (VII). This was reduced catalytically or by means of sodium in dry amyl alcohol to the required 4-n-*propylamino*-3-(4′-*diethylamino*-1′-*methylbutyl*)*aminoanisole* (III), which possessed the usual properties of this type of substance, being particularly susceptible to atmospheric oxidation and not readily yielding crystalline salts.

The product (III) showed only slight schizonticidal activity when administered subcutaneously at the maximum tolerated dose to chicks infected with *Plasmodium gallinaceum*, and it was ineffective by oral administration against *P. relictum* in canaries.

Experimental.*

(Melting points are corrected.)

3-*Nitro*-4-(N⁴-*acetylsulphanilamido*)*anisole*.—*p*-Acetamidobenzenesulphonyl chloride (500 g.) was added with cooling to 3-nitro-4-aminoanisole (300 g.) in pyridine (1050 c.c.). After 24 hours the sulphonamide was precipitated by pouring the reaction mixture into water (7 l.). Dilution of a solution of the crude product in 2N-sodium hydroxide (900 c.c.) with water (8 l.) precipitated an impurity, probably the disulphonamide, which was removed. Acidification of the filtrate with 2N-hydrochloric acid precipitated the required *sulphonamide*, m. p. 173—174°, 549 g. (84% yield) (Found: N, 11·5. $C_{15}H_{15}O_5N_3S$ requires N, 11·5%).

The corresponding *p*-toluenesulphonamide, prepared in a similar manner (90% yield), formed a less soluble sodium salt. It separated from methanol as yellow rhombs, m. p. 102—103° (m. p. 103·5—104° when prepared by direct nitration; Simonov, *loc. cit.*) (Found: N, 8·9. Calc. for $C_{14}H_{14}O_5N_3S$: N, 8·7%).

3-*Nitro*-4-(N⁴-*acetyl*-N¹-n-*propylsulphanilamido*)*anisole*.—*n*-Propyl bromide (539 c.c.) was added to 3-nitro-4-(N⁴-acetylsulphanilamido)anisole (869 g.) dissolved in 2N-sodium hydroxide (1507 c.c.) and alcohol (550 c.c.) and the mixture was refluxed for 16 hours. It was then stirred into a mixture of water (10 l.) and 2N-sodium hydroxide (1 l.). 3-*Nitro*-4-(N⁴-*acetyl*-N¹-n-*propylsulphanilamido*)*anisole* which separated was washed with water and crystallised twice from methanol (3 l.) as light brown irregular prisms, m. p. 147—149°, 610 g. (63% yield) (Found: N, 10·4; OMe, 7·8. $C_{17}H_{19}O_5N_3S$(OMe) requires N, 10·3; OMe, 7·6%).

3-*Nitro*-4-(N-n-*propyl*-p-*toluenesulphonamido*)*anisole*.—3-Nitro-4-(*p*-toluenesulphonamido)anisole (644 g.) was treated with 2N-sodium hydroxide (1 l.), water (1·5 l.) and ethyl alcohol (1 l.) and the resulting suspension of sodium salt refluxed for 18 hours with propyl bromide (492 g.). 3-*Nitro*-4-(N-n-*propyl*-p-*toluenesulphonamido*)*anisole* was isolated by the addition of water (3 l.) and 2N-sodium hydroxide (1 l.), and crystallised twice from ethyl alcohol as lemon-yellow prisms, m. p. 108—109°, 562 g. (77% yield) (Found: N, 7·8; OMe, 8·7. $C_{16}H_{17}O_4N_3S$(OMe) requires N, 7·7; OMe, 8·5%).

3-*Nitro*-4-n-*propylaminoanisole*.—(a) *Hydrolysis of* 3-*nitro*-4-(N⁴-*acetyl*-N¹-n-*propylsulphanilamido*)*anisole*. This sulphonamide (82 g.) was refluxed for 1 hour with a mixture of sulphuric acid (140 g. diluted to 200 c.c. with water) and glacial acetic acid (100 c.c.). A slow stream of nitrogen was passed through an identical hydrolysis on $\frac{1}{10}$ this scale and the effluent gas scrubbed with 2N-sodium hydroxide solution. No brown gases were evolved and the alkaline liquor in the traps gave a negative reaction for nitrate or nitrite. The dark red cold hydrolysis liquor was made alkaline (phenolphthalein) with 50% sodium hydroxide solution and the separated red oil extracted with three 1 l. portions of chloroform. The combined extracts were dried over potassium carbonate, the chloroform removed, and the residue fractionated using an electrically heated Vigreux column. Two fractions were obtained. One, a faintly red liquid, b. p. 65°/0·02 mm., $n_D^{20°}$ 1·5445, 4·0 g. (12% yield), proved to be 4-n-*propylaminoanisole* (Found: C, 72·8; H, 9·1; N, 8·8; OMe, 18·9, 18·7. $C_9H_{13}N$(OMe) requires C, 72·7; H, 9·1; N, 8·5; OMe, 18·8%). The identity of this fraction was established by the preparation in pyridine of its p-*toluenesulphonamido*-derivative, which crystallised from light petroleum (b. p. 40—60°) in well-defined colourless rectangular rods, m. p. 53—55°, mixed m. p. 53—54° with 4-(*N*-*n*-propyl-*p*-toluenesulphonamido)anisole prepared by *n*-propylating 4-*p*-toluenesulphonamidoanisole (Reverdin, *Ber.*, 1909, **42**, 1523) (Found: C, 64·3; H, 6·9; N, 4·4; S, 10·2. $C_{17}H_{21}O_5NS$ requires C, 64·0; H, 6·6; N, 4·4; S, 10·05%). The other fraction, a deep red oily liquid, b. p. 120°/0·02 mm., 30 g. (71% yield) was 3-*nitro*-4-n-*propylaminoanisole* (Found: C, 57·0; H, 6·8; N, 13·5; OMe, 15·1. $C_9H_{11}O_3N_3$(OMe) requires C, 57·1; H, 6·7; N, 13·3; OMe, 14·8%).

(b) *Hydrolysis of* 3-*nitro*-4-(N-n-*propyl*-p-*toluenesulphonamido*)*anisole*. This sulphonamide (91 g.) was refluxed for 1 hour with a mixture of sulphuric acid (175 g. diluted to 250 c.c. with water) and glacial acetic acid (400 c.c.). A slow stream of air was passed through the reaction mixture and then bubbled through a train of 3 absorption tubes, each containing 20 c.c. of 2N-sodium hydroxide. As the hydrolysis progressed brown gases were evolved. The apparatus was swept out with air at the end of the experiment and the bulked contents of the first two tubes analysed (total nitrogen, 0·09 g., which corresponded to 20% of the calculated quantity of nitrogen eliminated in the formation of the 5·1 g. of 4-*n*-propylaminoanisole isolated (see below). Nitrate absent. Nitrite, by permanganate titration, exactly equivalent to 0·09 g. nitrogen). Quantitative absorption of the gases evolved during the hydrolysis was not attempted.

The hydrolysis liquor was basified and extracted with chloroform as before. Fractionation of the product again yielded two fractions. One, a faintly red liquid, b. p. 65°/0·02 mm., $n_D^{22°}$ 1·5465, 5·1 g. (12% yield), analysed, as expected, for 4-*n*-propylaminoanisole (Found: N, 8·7; OMe, 18·9. Calc. for $C_9H_{13}N$(OMe): N, 8·5; OMe, 18·8%). The high-boiling fraction, 3-nitro-4-*n*-propylaminoanisole, was obtained in 62% yield, b. p. 120°/0·02 mm.

(c) *Alternative preparation*. 4-Bromo-3-nitroanisole (8·4 g.) (Samant, *Ber.*, 1942, **75**, 1008) was heated with *n*-propylamine (4·3 g., 2·0 mol.) in a sealed tube at 120—130° for 7½ hours. The oily product was washed with water to remove unchanged propylamine and an equal volume of concentrated hydrochloric acid was then added. Unchanged bromo-compound was removed by filtration. The filtrate was ether washed, basified, and the liberated red oil extracted with ether. The extract was dried (Na_2SO_4), evaporated, and distilled in a bulb tube at 130°/0·05 mm., yielding a dark red oil (1·5 g.). This was identified by stannous chloride reduction to 3-amino-4-*n*-propylaminoanisole, identical (mixed m. p.) with that prepared *via* the sulphonamide.

3-*Amino*-4-n-*propylaminoanisole*.—(a) *Stannous chloride reduction*. 3-Nitro-4-*n*-propylaminoanisole (37 g.) was dissolved in concentrated hydrochloric acid (56 c.c.) and treated portionwise with a solution of stannous chloride (150 g.) in concentrated hydrochloric acid (112 c.c.). The vigorous reaction was controlled by cooling. When it ceased the resultant suspension was heated until complete solution was effected, cooled, and basified with a large excess of well-cooled 50% sodium hydroxide solution while still supersaturated. The liberated base was taken up in ether and the extract evaporated, leaving a dark mobile product; 3-*amino*-4-n-*propylaminoanisole* crystallised from light petroleum (b. p. 80—100°) (charcoal) as colourless needles, m. p. 62°, 13 g. (41% yield), which, like the petroleum liquors, very rapidly developed a red colour when in contact with the atmosphere (Found: C, 66·4; H, 8·9; N, 15·6. $C_{10}H_{16}ON_2$ requires C, 66·6; H, 8·9; N, 15·55%).

(b) *Catalytic reduction*. 3-Nitro-4-*n*-propylaminoanisole (20 g.) dissolved in dioxan (200 c.c.) was hydrogenated in the presence of 5% Adams's catalyst at 20°/5 atmospheres. The product was distilled and the fraction, b. p. 110°/0·05 mm., a yellow oil, 13·5 g. (78% yield), was collected, when it crystallised; m. p. 59—61° (Found: OMe, 17·7. $C_9H_{12}N_2$(OMe) requires OMe, 17·2%).

4-n-*Propylamino*-3-(4′-*diethylamino*-1′-*methylbutyl*)*aminoanisole*.—3-Amino-4-*n*-propylaminoanisole (13·5 g.) was condensed with 5-diethylamino-2 : 2-diethoxypentane (25 g.) in the presence of ammonium chloride (0·5 g.). The condensation mixture was stirred under an atmosphere of hydrogen, the internal temperature being raised from 130° to 190° during 2 hours. Practically the theoretical quantity of alcohol distilled. Low-boiling material up to 150° (internal temperature)/15 mm. was removed, leaving the crude anil (VII) which was dissolved in dioxan (300 c.c.) and hydrogenated in the presence of 10% Adams's catalyst at 25°/30 atmospheres. Only 60% of the theoretical uptake of hydrogen was realised, even when fresh catalyst was introduced. The partially reduced anil was recovered and reduced with sodium

* This work was first carried out in 1943 but the records were destroyed by enemy action.

(40 g.) in dry amyl alcohol (900 c.c.). An atmosphere of hydrogen was maintained in the reaction vessel during the ensuing operations. The reduction mixture was acidified (Congo red) with concentrated hydrochloric acid and warmed to hydrolyse unchanged anil. It was then neutralised (litmus) and the amyl alcohol removed by rapid steam distillation. The residue was made alkaline (phenolphthalein) and exhaustively ether extracted. The extract was dried (K_2CO_3), and fractionated by means of an electrically heated Vigreux column. The fraction, b. p. 145°/0·03 mm., was a light yellow oil (6·7 g.), which proved to be the required 4-n-*propylamino*-3-(4′-*diethylamino*-1′-*methylbutyl*)*aminoanisole* (III). It rapidly turned red in air (Found: C, 70·6; H, 10·7; N, 12·5; OMe, 9·2. $C_{18}H_{32}N_2(OMe)$ requires C, 71·0; H, 10·8; N, 13·1; OMe, 9·65%).

The authors wish to express their indebtedness to Mr. S. Bance, B.Sc., A.R.I.C., for the semi-microanalyses, to the Biological Division, May & Baker Ltd., for the biological results, and to the Directors of Messrs. May & Baker Ltd. for permission to publish the results.

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[*Received, December 21st*, 1945.]

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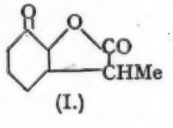
127. *The Constitution of Santonin. Part IV.*

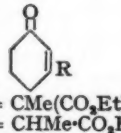
By G. R. CLEMO, WESLEY COCKER, and STANLEY HORNSBY.

All attempts to prepare the lactone of 2-hydroxy-3-keto*cyclo*hexyl-α-propionic acid (I) by the method of Paranjape, Phalnikar, Bhide, and Nargund (*Current Science*, 1943, **12**, 150; *Rasayanam*, 1943, **1**, 233) from 3-chloro-Δ²-*cyclo*hexen-1-one and ethyl sodiomethylmalonate followed by cyclisation of the ester with sulphuric acid were unsuccessful; 3-ethyl-Δ²-*cyclo*hexen-1-one (IV) was invariably obtained.

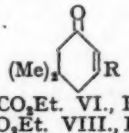
In view of the work done in these laboratories since 1929 on santonin and related sesquiterpenes we were interested in the asymmetric synthesis of *l*-santonin claimed by Paranjape, Phalnikar, Bhide, and Nargund (*Nature*, 1944, **153**, 141). Fuller details of the synthesis were given later and lactone (I) was stated to be obtained at an early stage of the synthesis. Unfortunately we have been unable to consult the second paper referred to in the summary above, but the abstract (*Chem. Abs.*, 1944, **38**, 4266) gives sufficient information to enable a repetition of the work to be attempted.



(I.)



[II., R = $CMe(CO_2Et)_2$.
III., R = $CHMe{\cdot}CO_2Et$.
IV., R = Et.]



[V., R = $CH_2{\cdot}CO_2Et$. VI., R = $CH(CO_2Et)_2$.
VII., R = $CHMe{\cdot}CO_2Et$. VIII., R = $CMe(CO_2Et)_2$.
IX, R = Et.]

In the method described by the Indian workers 3-chloro-Δ²-*cyclo*hexen-1-one (Crossley and Haas, *J.*, 1903, **83**, 498) was condensed in benzene with ethyl sodiomethylmalonate to give ethyl Δ²-*cyclo*hexen-1-one-3-methylmalonate (II) and this, on treatment with 6N-sulphuric acid in 50% aqueous alcohol, was stated to cyclise to the lactone (I).

Several attempts by the present authors to repeat this work have failed to yield (I) and in every case an almost quantitative yield of 3-ethyl-Δ²-*cyclo*hexen-1-one (IV) was obtained.

A similar result was reported by Crossley and Gilling (*J.*, 1909, **95**, 24), who obtained *iso*phorone by the hydrolysis of ethyl 5 : 5-dimethyl-Δ²-*cyclo*hexen-1-one-3-acetate (V) with alcoholic potash, and 5 : 5-dimethyl-3-ethyl-Δ²-*cyclo*hexen-1-one (IX) from ethyl 5 : 5-dimethyl-Δ²-*cyclo*hexen-1-one-3-α-propionate (VII) under similar conditions.

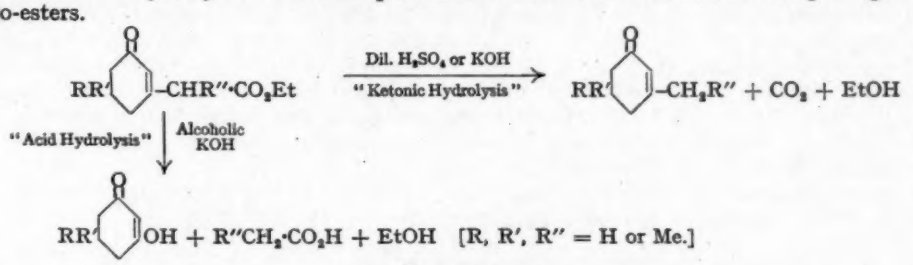
We have repeated and confirmed this work and similar results were obtained by hydrolysis of compounds (V) and (VII) with 6N-aqueous-alcoholic sulphuric acid. In addition, compounds (III), (VI), and (VIII) respectively gave 3-ethyl-Δ²-*cyclo*hexen-1-one, *iso*phorone, and 5 : 5-dimethyl-3-ethyl-Δ²-*cyclo*hexen-1-one on treatment with either acid or alkali.

Decarboxylation in varying degree took place during the attempted cyclisation of all these esters with ice-cold 60%, 80%, or concentrated sulphuric acid, a proportion of the starting material being recovered. There was no evidence of the formation of any lactone.

Attempts made to prepare the acids corresponding to the esters (III), (V), and (VII) by hydrolysis with cold 6% alcoholic potash were unsuccessful. In every instance decarboxylation to a greater or less extent was experienced and we must conclude that even the potassium salts of the required acids are extremely labile. When, however, these esters are refluxed with 10% alcoholic potash small amounts of dihydroresorcinol and dimedon are respectively isolated in addition to the ketones already mentioned.

Compounds (II), (VI), and (VIII) were never obtained pure. On condensation of 3-chloro-Δ²-*cyclo*hexen-1-one or 3-chloro-5 : 5-dimethyl-Δ²-*cyclo*hexen-1-one with ethyl sodiomalonate or ethyl sodiomethylmalonate in dry benzene partial decarboxylation always appeared to take place and difficultly separable mixtures of compounds (II) and (III), (V) and (VI), and (VII) and (VIII) were obtained. If the condensations were carried out in alcohol the principal products were compounds (III), (V), and (VII), since under these circumstances alcoholysis took place with the formation of ethyl carbonate (compare Crossley and Gilling, *Proc.*, 1908, **24**, 130; 1909, **25**, 96).

The total decarboxylation of all these esters on hydrolysis is not surprising since in every case there is a system similar to that of a β-keto-ester, for the double bond α : β to the keto group is virtually a second carbonyl group, and hence, on hydrolysis with acid or dilute alkali, " ketonic hydrolysis " takes place. In addition, however, some " acid hydrolysis " also takes place under alkaline conditions, thus completing the analogy with the β-keto-esters.



$RR'C_6H_7O\text{-}CHR''\cdot CO_2Et \xrightarrow{\text{Dil. } H_2SO_4 \text{ or KOH}} RR'C_6H_7O\text{-}CH_2R'' + CO_2 + EtOH$

$RR'C_6H_7O\text{-}CHR''\cdot CO_2Et \xrightarrow{\text{Alcoholic KOH}} RR'C_6H_7O\text{-}OH + R''CH_2\cdot CO_2H + EtOH$ [R, R', R'' = H or Me.]

Experimental.

Ethyl Δ²-cyclo*Hexen*-1-*one*-3-*methylmalonate* (II).—As no details of the preparation of this compound are given in the abstract its preparation is described. Ethyl methylmalonate (5·3 g.) was added drop by drop to a stirred suspension of sodium (0·7 g.) in boiling benzene (50 c.c.) and the mixture was refluxed until no metallic sodium remained. Then 3-chloro-Δ²-*cyclo*hexene-1-one (4·0 g.) was slowly added, and stirring and boiling continued for 5 hours. The benzene was distilled off, and the residue acidified with cold dilute acetic acid and extracted thrice with ether. The dried extract was distilled and collected at 184—190°/2 mm. On redistillation it had b. p. 174°/2 mm. (1·4 g.) (Found: C, 64·0; H, 7·5. Calc. for $C_{14}H_{20}O_5$: C, 62·7; H, 7·5%).

3-*Ethyl*-Δ²-cyclo*hexen*-1-*one*.—The above compound was heated for 6 hours with 6N-sulphuric acid in 50% aqueous alcohol (14 c.c.), the alcohol was removed in a vacuum, and the residue was poured into water and extracted with ether. The extract after drying was distilled, giving 0·55 g. (84% of theory), b. p. 73—75°/1—2 mm. (Blaise and Maire, *Bull. Soc. chim.*, 1908, **4**, 419, give b. p. 83°/8 mm.) (Found: C, 76·8; H, 9·6. Calc. for $C_8H_{12}O$: C, 77·4; H, 9·7%). The *semicarbazone* prepared in the usual way crystallised from aqueous alcohol as plates, m. p. 191—192°; this is possibly a stereoisomeric form of that described by Blaise and Maire (*loc. cit.*) who give m. p. 240° (Found: C, 59·8; H, 8·2. $C_9H_{15}ON_3$ requires C, 59·7; H, 8·3%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol as scarlet needles, m. p. 133—134° (Found: C, 55·5; H, 5·5. $C_{14}H_{16}O_4N_4$ requires C, 55·3; H, 5·3%).

Ethyl 5 : 5-*Dimethyl*-Δ²-cyclo*hexen*-1-*one*-3-*malonate* (VI).—3-Chloro-5 : 5-dimethyl-Δ²-*cyclo*hexene-1-one (5 g., Crossley and Le Sueur, *J.*, 1903, **83**, 117) was added to a stirred suspension of ethyl sodiomalonate (from ethyl malonate (5·1 g.) and sodium (0·73 g.)), in benzene (25 c.c.), and the mixture was refluxed overnight. The reaction mixture was treated as described above and a colourless oil (3·5 g., b. p. 168—170°/3 mm.) was isolated.

iso*Phorone*.—The above ester (1·7 g.) was refluxed for 6 hours with 30% aqueous-alcoholic sulphuric acid (17 g.). *iso*Phorone (0·8 g., 95% of theory), b. p. 78°/3 mm., was obtained. Its 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in scarlet plates, m. p. 129—130° (Found: C, 56·5; H, 5·2. $C_{15}H_{18}O_4N_4$ requires C, 56·6; H, 5·6%).

Ethyl 5 : 5-*Dimethyl*-Δ²-cyclo*hexen*-1-*one*-3-*methylmalonate* (VIII).—This was obtained as a colourless oil, b. p. 170°/4 mm. (Found: C, 65·9; H, 8·4. $C_{16}H_{24}O_5$ requires C, 64·9; H, 8·1%), by a method similar to those described above. On hydrolysis with 6N-sulphuric acid in 50% alcohol it gave 5 : 5-dimethyl-3-ethyl-Δ²-*cyclo*hexen-1-one, b. p. 105—106°/5 mm., in almost quantitative yield. It gave a semicarbazone, m. p. 197°, identical with that obtained by Crossley and Gilling (*loc. cit.*).

One of us (S. H.) thanks the Council of King's College for the award of a post-graduate Scholarship.

University of Durham, King's College, Newcastle-upon-Tyne, 2. [*Received, January 2nd*, 1946.]

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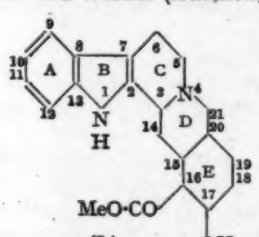
128. *The Constitution of Yohimbine. Part I.*

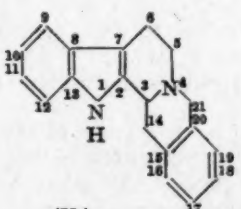
By G. R. Clemo and G. A. Swan.

The structure (V) for yobyrine, a selenium dehydrogenation product of yohimbine, has been proved by synthesis. A base having structure (X) has also been synthesised; on dehydrogenation with palladium, this gave (V). The " carboline-blue " colour reaction described by Harvey, Miller, and Robson (*J.*, 1941, 153) is discussed.

The constitution of the alkaloid yohimbine has been largely elucidated by the work of Barger and Scholz (*Helv. Chim. Acta*, **1933**, **16**, 1343; **1935**, **18**, 923), Wibaut and van Gastel (*Rec. Trav. chim.*, **1935**, **54**, 85), and Hahn and Werner (*Annalen*, **1935**, **520**, 123), the probable structure being represented by (I).



(I.)

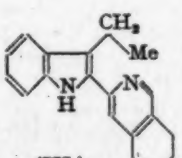


(X.)

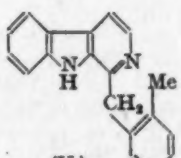
(II.) double bond at C_3–C_{14}

(IV.) " " "

C=O at position 21



(III.)

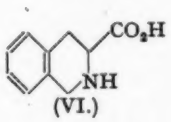


(V.)

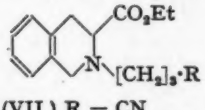
On dehydrogenation with selenium, yohimbine gives rise to yobyrine, $C_{19}H_{16}N_2$, " tetrahydroyobyrine," $C_{19}H_{20}N_2$, and ketoyobyrine, $C_{20}H_{16}ON_2$ (Mendlik and Wibaut, *Rec. Trav. chim.*, 1929, **48**, 191; 1931, **50**, 91; Wibaut and van Gastel, *loc. cit.*; Barger and Scholz, *Helv. Chim. Acta*, 1933, **16**, 1343). The last authors represented the first two of these substances by formulæ (II) and (III) respectively.

Recently an important contribution to the chemistry of the alkaloid has been made (Witkop, *Annalen*, 1943, **554**, 83; Pruckner and Witkop, *ibid.*, p. 127) which has clarified many hitherto unexplained points. Structure (II) for yobyrine is unsatisfactory, as one would not have expected the dehydrogenation to have stopped at this stage. Witkop has suggested the alternative (V), which is in all respects entirely satisfactory (*e.g.*, it explains the salts of yobyrine being colourless, and showing a blue fluorescence in solution, as it is a derivative of β-carboline). Witkop's conclusions are based on degradation and absorption spectra; but we have approached the problem from the synthetic point of view.

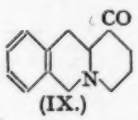
The condensation of phenylalanine with formaldehyde to give 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylic acid (VI) has been described by Pictet and Spengler (*Ber.*, 1911, **44**, 2030). We have condensed the



(VI.)

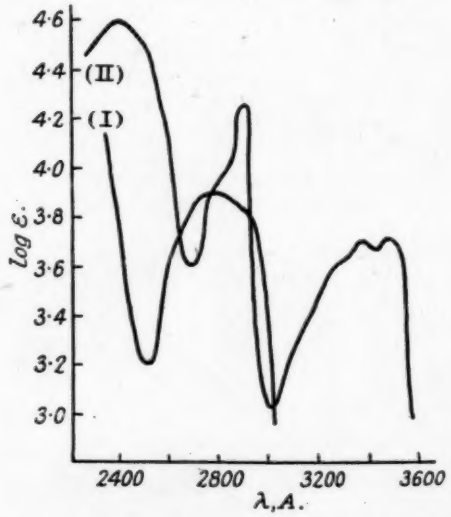


(VII.) R = CN
(VIII.) R = CO_2Et

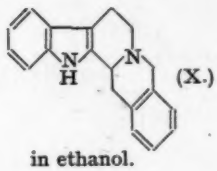


(IX.)

ethyl ester of this acid with γ-bromopropyl cyanide to give *ethyl* 2-(*γ-cyanopropyl*)-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline-3-carboxylate* (VII), which was alcoholysed to *ethyl* 2-(*γ-carbethoxypropyl*)-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline-3-carboxylate* (VIII). By carrying out the Dieckmann reaction on this diester, we obtained 1-*keto*-7 : 8-*benzo*-1 : 2 : 3 : 4 : 6 : 9-*hexahydropyridocoline* (IX), the *phenylhydrazone* of which underwent the Fischer indole reaction, giving 7 : 8-*benzo*-1 : 2-(2′ : 3′-*indolo*)-3 : 4 : 6 : 9-*tetrahydropyridocoline* (X), a colourless, crystalline solid, m. p. 196—197°. A solution of this base in alcohol, or of its hydrochloride in water, contained in a quartz vessel, gave a blue fluorescence when placed in a beam of ultra-violet radiation (this was not observed in a glass vessel). The ultra-violet absorption spectrum is shown in the accompanying figure (Curve I). The



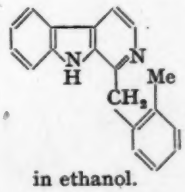
Curve (I)



(X.)

in ethanol.

Curve (II)



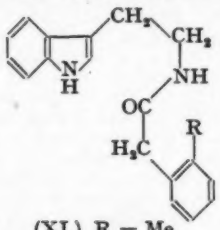
in ethanol.

base (V), gave only a pale yellow colour with *p*-dimethylaminobenzaldehyde in dilute hydrochloric acid in the cold; but, on heating, a pink colour developed, which faded on cooling. This reversible colour change could be repeated indefinitely, and is given by 2 : 3-dimethylindole and by tetrahydroharmine (Perkin and Robinson, *J.*, 1919, **115**, 939).

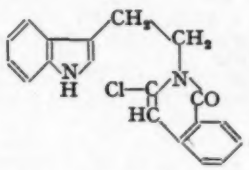
When (X) was heated with palladium black it was converted into a mixture of bases, from which a base *A* was isolated. *A* was a colourless, crystalline solid, m. p. 216—217° (corr.), and seemed to correspond to yobyrine. It might conceivably have the structure (II) suggested for yobyrine by Barger and Scholz. However, this was disproved by the following synthesis.

For this, *o*-tolylacetic acid was required. The best method found in the literature for the preparation of this compound is that of Hill, Short, and Stromberg (*J.*, 1937, 937), by the oxidation of *o*-allyltoluene. We found it more convenient to make use of the reaction first described by Arndt and Eistert (*Ber.*, 1935, **68**, 200); and from *o*-toluoyl chloride obtained a 53% yield of the required acid. When this was condensed with 3-(β-aminoethyl)indole (tryptamine), it gave 3-[β-(*o-tolylacetamido*)*ethyl*]*indole* (XI), which, in the presence of phosphoryl chloride, underwent ring closure to give a product which was dehydrogenated in the presence of palladium black, yielding a base *B*, m. p. 216—217° corr.), whose structure is clearly represented by 2-(*o*-

methylbenzyl)-β-*carboline*. Bases *A* and *B* are identical, and no depression of melting point was observed on admixture. A specimen of yobyrine obtained from the alkaloid was not available for comparison; but there is



(XI.) R = Me
(XIII.) R = CO_2H
(XIV.) R = OMe

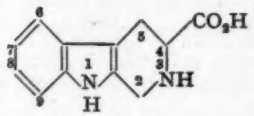


(XII.)

no doubt of the identity of this base (*A* or *B*) with yobyrine. Solutions of the base in alcohol, or of its hydrochloride in water, exhibit a strong blue-violet fluorescence. The melting points of the base, the *picrate*, and the methiodide agree with those recorded for yobyrine; as does the ultra-violet absorption spectrum (Curve II) (cf. Witkop, *loc. cit.*). Moreover, oxidation of our base with selenium dioxide gave a product whose melting point corresponds to that of yobyrone.

We have also carried out preliminary attempts to synthesise the yohimbine ring system by a number of other methods. (1) By condensing ethyl ω-bromo-*o*-toluate with sodium methoxide, followed by hydrolysis, *ω-methoxy-o-toluic acid* was obtained. This we had hoped to subject to the Arndt–Eistert reaction to obtain an acid which, when condensed with tryptamine, might yield an amide (XIV) capable of cyclisation to give the yohimbine skeleton. However, attempts to prepare the chloride of this acid failed: under mild conditions, the acid was unattacked, whilst under more vigorous conditions, phthalide resulted. (2) Tryptamine was condensed with homophthalic acid to give *homophthal*-(β-3-*indolylethyl*)*imide*. Attempts to cyclise this with phosphoryl chloride to give (IV), however, resulted in a *compound* which is probably 3-chloro-2-(β-indolylethyl)-1-*iso*quinolone (XII) (cf. Haworth, Perkin, and Pink, *J.*, **1925**, **127**, 1709). (3) Tryptamine was condensed with homophthalic anhydride to give a *compound* which is probably an *N*-(β-indolylethyl)homophthalamic acid (XIII). This was esterified by the action of methyl iodide on the silver salt, and then treated with phosphoryl chloride. From the reaction mixture was isolated a product in yield too small to permit of a full investigation; but which may, perhaps, be represented by (IV). (4) Attempts to cyclise 3-*formyl*-2-*benzyl*-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline* with phosphoryl chloride or phosphoric oxide have not given any promising results.

Location of the Carbomethoxy Group in the Yohimbine Molecule.—The suggestion, made by Harvey, Miller, and Robson (*loc. cit.*), that the carbomethoxy group is present at position 5 is attractive in so far as this structure might arise from tryptophan. The evidence of these authors is based solely on a colour reaction with concentrated sulphuric acid containing an oxidising agent. A blue colour is first produced and this slowly gives way to an olive-green, which in turn is replaced by a permanent yellow, the final solution possessing a faint green fluorescence. They carried out this test on a series of compounds and concluded that it was indicative of the presence of a β-carboline nucleus, hydrogenated at positions 2, 3, 4 and 5 and carrying a carboxyl group at position 4 (XV). It is, however, significant that out of a list of fourteen derivatives of 2 : 3 : 4 : 5-tetrahydro-β-carboline to which they subjected the test, ten have a carboxyl or carbomethoxy group at position 4, whilst the remaining four did give the test in a transient manner. This evidence seemed to us scarcely sufficient to warrant the generalisation which these authors made, so we have extended the list to include the following derivatives of 2 : 3 : 4 : 5-tetrahydro-β-carboline; the 2-methyl (Hahn and Hansel, *Ber.*, **1938**, **71**, 2163), 2-benzyl (Hahn and Ludewig, *Ber.*, **1934**, **67**, 2031; Hahn and Hansel, *Ber.*, **1938**, **71**, 2192), and 2-(*o*-methylbenzyl) compounds, as well as our base (X). Although in none of these compounds is a carboxyl group present, with each we obtained a series of colour changes similar to those described by Harvey, Miller, and Robson. Moreover, Dewar and King (*Nature*, **1941**, **148**, 25) have obtained similar colour transformations with the carboxyl-free yohimbone (this compound, which they designated yohimbol, was subsequently shown by Witkop to be a ketone) and have pointed out that this entirely invalidates the evidence on which the suggested alternative formula rests. Our results are in accord with this; and Witkop has shown that the results of his work on the Oppenauer dehydrogenation of yohimbine are best explained by a structure in which the hydroxyl group is in the β-position to the carboxyl group, as in (I).



(XV.)

Harvey, Miller, and Robson have suggested that the blue pigment formed in the above colour test reaction may be 4 : 5-dihydro-β-carboline-4-carboxylic acid. This seems to us unlikely; another possibility is that the colour may be due to a semiquinone (cf. Weiss, *J.*, **1942**, 245).

Further work in this field is in hand.

Experimental

dl-N-*Benzoylphenylalanine*.—The azlactone of α-benzamidocinnamic acid (20 g.)(Erlenmeyer, *Annalen*, **1893**, **275**, 1) was suspended in 95% alcohol (300 c.c.) and heated to 75°. Sodium amalgam (100 g., 4%) was added and the mixture stirred for 1½ hours; a similar portion of amalgam was then added, and stirring continued for a further 2½ hours. The liquid was filtered hot, the bulk of the alcohol distilled off (water-bath), and the residue dissolved in water and acid-

ified with hydrochloric acid. The resulting solid was collected and dissolved in hot alcohol, and the solution filtered and diluted with an equal volume of hot water; on cooling, the product separated (13·5 g., m. p. 182°).

Ethyl 1 : 2 : 3 : 4-*Tetrahydroisoquinoline*-3-*carboxylate*.—A mixture of the above (10 g.) and concentrated hydrochloric acid (50 c.c.) was heated in a sealed bulb in the water-bath for 30 hours. Benzoic acid was removed from the reaction product by steam-distillation, and the residue evaporated to dryness under reduced pressure (water-bath). The resulting solid was dissolved in a hot mixture of water (100 c.c.) and ammonia (10 c.c., *d* 0·88), the solution filtered, excess of ammonia removed by concentration under reduced pressure (water-bath), and the resulting solution added to one of copper acetate (4 g.) in hot water (60 c.c.). After having been kept overnight in the refrigerator, the precipitated copper salt was collected, washed with cold water, suspended in boiling water (200 c.c.), and decomposed by hydrogen sulphide. The copper sulphide was filtered off from the hot solution and extracted with boiling water; the combined filtrate and washings were evaporated to dryness under reduced pressure (water-bath). The residue was suspended in concentrated hydrochloric acid (50 c.c.) and methylal (10 c.c.) was added. After having been kept overnight at room temperature, the mixture was heated for 24 hours on the water-bath and evaporated to complete dryness under reduced pressure (water-bath), the last traces of water being removed by adding a little absolute alcohol and then distilling it off. Absolute alcohol (40 c.c.) was added to the resulting solid, and the cooled mixture saturated with dry hydrogen chloride and refluxed for 3 hours (water-bath). Alcohol was then removed (water-bath), the residue dissolved in a small volume of cold water, and the solution saturated with sodium carbonate and extracted with ether. Ether was removed from the dried (K_2CO_3) extract, and the residue distilled, the fraction, b. p. 110—130°/1 mm. (1·4 g.), being collected. The *ester* is a colourless liquid, b. p. 120°/1 mm. (Found: C, 70·2; H, 7·7. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·3%). The *picrate* separated from alcohol as yellow crystals, m. p. 204° (Found: C, 50·3; H, 4·2. $C_{12}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 50·0; H, 4·2%). The picrolonate separated from alcohol as clusters of yellow needles, m. p. 212—213°.

Ethyl 2-(γ-*Cyanopropyl*)-1 : 2 : 3 : 4-*tetrahydroisoquinoline*-3-*carboxylate* (VII).—A mixture of the above ester (4 g.), γ-bromopropyl cyanide (3 g.) (Derick and Hess, *J. Amer. Chem. Soc.*, 1918, **40**, 547) and anhydrous potassium carbonate (1·45 g.) was heated, with occasional stirring, for 5 hours in the water-bath. After cooling, water (30 c.c.) was added, the mixture extracted with ether, the extract dried (K_2CO_3), the ether removed, and the residue fractionated at 1 mm., giving: (i) 1 g., b. p. below 140°; (ii) 2·3 g., b. p. 150—190°. On redistillation, the latter gave the *cyanide* as a yellow, viscous liquid, b. p. 170°/1 mm. (Found: C, 70·55; H, 7·7. $C_{16}H_{20}O_2N_2$ requires C, 70·6; H, 7·3%).

Ethyl 2-(γ-*Carbethoxypropyl*)-1 : 2 : 3 : 4-*tetrahydroisoquinoline*-3-*carboxylate* (VIII).—A solution of the above cyanide (2·3 g.) in absolute alcohol (14 c.c.) was cooled in ice and saturated with dry hydrogen chloride. The resulting solution was refluxed for 7 hours (water-bath) and evaporated to dryness under reduced pressure (water-bath), and the residue was dissolved in cold water, basified (sodium carbonate), and extracted with ether. The ether was removed from the dried (K_2CO_3) extract and the residue distilled, giving the *diester* as a pale yellow, viscous liquid (1·6 g., b. p. 170°/1 mm.) (Found: C, 68·0; H, 8·05. $C_{18}H_{25}O_4N$ requires C, 67·7; H, 7·85%).

1-*Keto*-7 : 8-*benzo*-1 : 2 : 3 : 4 : 6 : 9-*hexahydropyridocoline* (IX).—The above diester (1 g.) in toluene (2 c.c.) was added in the cold to powdered potassium (0·33 g.) under toluene (8 c.c.); the flask containing the mixture was plunged into a boiling water-bath and shaken for 2 minutes, after which it was left there for 1½ hours. After cooling, the excess of potassium was destroyed by the addition first of a few drops of alcohol, then of a few drops of water, after which concentrated hydrochloric acid (25 c.c.) was added, and the mixture heated in the water-bath for 3 hours. The liquid was then evaporated to dryness under reduced pressure (water-bath), the residue dissolved in water, basified (sodium carbonate) and extracted with ether. Ether was removed from the dried (K_2CO_3) extract, and the residue distilled as an orange-coloured oil which partly crystallised on cooling (0·28 g., b. p. 140°/1 mm.). This was stirred with a small volume of dry ether, and the yellow crystalline solid collected and washed with a little ether (0·14 g., m. p. 98° after softening at 88°); when recrystallised from light petroleum (b. p. 60—80°) this gave the *ketone* as orange-coloured plates, m. p. 99—100° (Found: C, 77·7; H, 7·4. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·45%). The *oxime* was prepared by refluxing a solution of the ketone, hydroxylamine hydrochloride, and anhydrous sodium acetate in methanol for 2 hours (water-bath), distilling off the methanol, adding water to the residue, collecting the resulting solid, and washing with water; from methanol (charcoal) it separated in colourless prisms, m. p. 207—208° (Found: C, 72·45; H, 7·6. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·4%). When calcium carbonate was used instead of sodium acetate, the oxime *hydrochloride* was obtained; this separated from alcohol in colourless prisms, m. p. 221° (Found: C, 62·1; H, 6·5. $C_{13}H_{17}ON_2Cl$ requires C, 61·8; H, 6·7%). The *phenylhydrazone* was prepared by heating a solution of the ether-washed ketone (0·14 g.) in absolute alcohol (2 c.c.) with phenylhydrazine (0·2 g.) for 2 hours on the water-bath, concentrating the solution, keeping it in the refrigerator, and collecting the resulting solid; when recrystallised from methanol, this afforded yellow prisms, m. p. 92°, softening at 80° (0·17 g.) (Found: C, 73·9; H, 7·8. $C_{19}H_{21}N_3,CH_3OH$ requires C, 74·3; H, 7·75%).

7 : 8-*Benzo*-1 : 2-(2′ : 3′-*indolo*)-3 : 4 : 6 : 9-*tetrahydropyridocoline* (X).—The above phenylhydrazone (0·13 g.) was dissolved by warming in absolute alcohol (4 c.c.), the solution cooled in ice, and saturated with dry hydrogen chloride. After having been kept for 1 hour at room temperature the solution was refluxed for 1½ hours (water-bath), the alcohol distilled off (water-bath), the residue cooled, and water added. The resulting yellow solid [60 mg., m. p. 298° (decomp.)] was collected, washed with water, and shaken with ether and dilute sodium hydroxide solution until all was dissolved. The ether layer was separated, dried (K_2CO_3), and the ether removed, when a solid (50 mg., m. p. 188—191°) remained. When recrystallised from methanol–water (charcoal) this afforded the *base* (X) as colourless needles, m. p. 196—197° (Found: C, 83·4; H, 6·6; N, 9·9. $C_{19}H_{18}N_2$ requires C, 83·2; H, 6·6; N, 10·2%). The picrate, prepared in alcoholic solution, separated from acetone–water as orange-yellow felted needles, m. p. 173—174°.

This base (20 mg.) was heated with palladium black (20 mg.) (Willstätter and Waldschmidt-Leitz, *Ber.*, 1921, **54**, 123) for 30 minutes at 225°/12 mm., when the greater part of the organic material sublimed. The product was dissolved in hot methanol, the solution boiled with charcoal, filtered, concentrated, and water added; on cooling, colourless needles, m. p. 216—217° (corr.), separated (Base *A*).

o-*Tolylacetic Acid*.—A solution of *o*-toluoyl chloride (1·5 g.) (Davies and Perkin, *J.*, 1922, **121**, 2207) in dry ether (10 c.c.) was added gradually with stirring to one of diazomethane (1·5 g.) in ether (80 c.c.) at 5°. After the mixture had been kept overnight at room temperature, the ether was removed under reduced pressure (finally at 30°). A solution of the residual, oily diazoketone in dioxan (10 c.c.) was added during 15 minutes to a stirred suspension of silver oxide (0·4 g.) in a solution of sodium carbonate (0·8 g.) and sodium thiosulphate (0·5 g.) in water (30 c.c.) at 55—60°. The temperature was kept at 55—60° for a further 1 hour and finally raised to 95° for 1 hour. Charcoal was then added to the diluted solution which was filtered hot. The cooled filtrate was acidified (dilute nitric acid), extracted with chloroform, the extract dried (Na_2SO_4), the chloroform removed, and the residue crystallised from water (charcoal), giving the acid as colourless plates, m. p. 88° (0·75 g.) (Found: C, 72·5; H, 6·35. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·65%).

3-[β-(o-*Tolylacetamido*)*ethyl*]*indole* (XI).—An intimate mixture of the above acid (0·52 g.) and 3-(β-aminoethyl)indole (0·52 g.) (Majima and Hoshino, *Ber.*, 1925, **58**, 2042) was heated for 30 minutes at 180—190°. After cooling, the residue was dissolved in hot methanol, and the solution boiled with charcoal, filtered, and cooled in ice; water was added dropwise with stirring until the solution just became turbid, when the *amide* soon separated as colourless plates, m. p. 99° (0·58 g.) (Found: C, 78·15; H, 6·85. $C_{19}H_{20}ON_2$ requires C, 78·10; H, 6·85%).

2-(o-*Methylbenzyl*)-β-*carboline* (V) *and* 2-(o-*Methylbenzyl*)-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline*.—The above amide (0·42 g.) was refluxed in dry benzene (20 c.c.) with phosphoryl chloride (0·9 c.c.) for 1 hour (water-bath), the benzene removed under reduced pressure (water-bath), and the residue boiled with dilute acetic acid; the resulting extract was filtered hot, cooled in ice, and basified with ammonia. The pale yellow precipitate (0·35 g.) was separated, washed with water, and dried as rapidly as possible in a vacuum desiccator. No attempt was made to purify this 2-(o-methylbenzyl)-4 : 5-dihydro-β-carboline, the crude material being used in the following experiments: (*a*) The base (50 mg.) was heated with palladium black (25 mg.) for 30 minutes at 180—190°/12 mm.; the product, worked up as described for the previous dehydrogenation, gave 2-(o-*methylbenzyl*)-β-*carboline* (Base *B*) (25 mg.) as colourless felted needles, m. p. 216—217° (corr.) after recrystallisation first from methanol–water, then from benzene (Found: C, 84·1; H, 6·05; N, 9·65. $C_{19}H_{16}N_2$ requires C, 83·8; H, 5·9; N, 10·3%). No depression of m. p. was observed on admixture with Base *A*. For yobyrine, Mendlik and Wibaut gave m. p. 217° (corr.). The *picrate*, prepared in alcoholic solution, separated from acetone–water as bright yellow crystals, m. p. 240° (decomp.) (Found: C, 60·0; H, 3·85. $C_{19}H_{16}N_2,C_6H_3O_7N_3$ requires C, 59·9; H, 3·8%). For yobyrine picrate, Witkop gave m. p. 239° (decomp.). When a solution of base *B* in dry acetone containing methyl iodide was kept, the methiodide separated as very pale yellow plates, m. p. 296° (decomp.). For yobyrine methiodide, Witkop gave m. p. 295°. When base *B* (90 mg.) in xylene (6 c.c.) was refluxed with freshly prepared selenium dioxide (90 mg.) for 2 hours, the solution decanted from the selenium, the xylene removed under reduced pressure (water-bath), and the residue distilled at 2 mm., an oil was obtained, which rapidly solidified, the *product* separating from methanol (charcoal) as yellow leaflets, m. p. 185° (Found: C, 79·85; H, 5·1. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9%). For yobyrone, Witkop gave m. p. 185°.

(*b*) A solution of the above dihydro base (0·3 g.) in absolute alcohol (15 c.c.) was refluxed on the water-bath while sodium (1·15 g.) was added during 15 minutes. After all the sodium had dissolved, the solution was diluted with water (15 c.c.) and the alcohol distilled off under reduced pressure (water-bath). The cooled solution was extracted with ether, the extract dried (K_2CO_3), the ether removed, the residue dissolved in methanol, and dry hydrogen chloride passed into the solution. On adding ether, a solid separated; this was collected, washed with ether [0·12 g., m. p. 260° (decomp.)] and treated with dilute sodium hydroxide solution; the product was extracted with ether, the extract dried (K_2CO_3) and the ether removed. The residue was recrystallised twice from methanol–water, giving colourless, rectangular tablets, m. p. 92—94° (Found: C, 77·75; H, 7·8. $C_{19}H_{20}N_2,H_2O$ requires C, 77·55; H, 7·5%). This is probably 2-(o-*methylbenzyl*)-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline*.

2-*Benzyl*-β-*carboline*.—2-Benzyl-2 : 3 : 4 : 5-tetrahydro-β-carboline was prepared by the method of Hahn and Hansel (*loc. cit.*) and from it we obtained a *picrate* separating from methanol–water as yellow needles, turning orange-coloured on drying on the water-bath, m. p. 215° (Found: C, 58·25; H, 4·4. $C_{18}H_{18}N_2,C_6H_3O_7N_3$ requires C, 58·65; H, 4·3%). The above authors gave m. p. 180° for the picrate. On heating with palladium black (20 mg.) for 30 minutes at 170—180° (12 mm.), this base (50 mg.) gave 2-*benzyl*-β-*carboline* as colourless leaflets, m. p. 177—178°, from methanol–water (30 mg.) (Found: C, 82·95; H, 5·55. $C_{18}H_{14}N_2$ requires C, 83·75; H, 5·45%). The solution of this base in alcohol–water or in dilute hydrochloric acid exhibited a blue-violet fluorescence. The *picrate*, prepared in alcoholic solution, separated from acetone–alcohol as bright yellow prisms, m. p. 235° (decomp.) (Found: C, 59·1; H, 3·5. $C_{18}H_{14}N_2,C_6H_3O_7N_3$ requires C, 59·15; H, 3·5%). The same base was also obtained by similarly dehydrogenating 2-benzyl-4 : 5-dihydro-β-carboline, prepared by the method of Hahn and Ludewig (*loc. cit.*).

ω-*Methoxy*-o-*toluic Acid*.—Ethyl ω-bromo-o-toluate (18 g.) (Davies and Perkin, *loc. cit.*) was added gradually, with shaking, to a solution of sodium (1·8 g.) in methanol (90 c.c.), cooled in ice. After the mixture had been refluxed for 2 hours, the precipitated sodium bromide was filtered off, the methanol removed (water-bath), and the residue cooled, diluted with water, and extracted with ether. Ether was removed from the dried (Na_2SO_4) extract, and the residue distilled. The distillate (9·7 g., b. p. 240—250°/760 mm.) was refluxed for 2 hours on the water-bath with a mixture of 95% alcohol (45 c.c.) and 40% sodium hydroxide solution (18 c.c.), the bulk of the alcohol distilled off (water-bath), and the residue diluted with water, cooled and acidified with concentrated hydrochloric acid. The *acid* (7·75 g., m. p. 92—93°) was collected, washed with water, dried, and recrystallised from benzene, giving colourless needles, m. p. 94° (Found: C, 65·15; H, 5·95. $C_9H_{10}O_3$ requires C, 65·1; H, 6·0%).

Homophthal-(β-3-*indolylethyl*)*imide*.—(i) A mixture of 3-(β-aminoethyl)indole (80 mg.) and homophthalic acid (90 mg.) (*Org. Synth.*, **22**, 61) was heated at 180° for 3 hours, and the residue recrystallised first from dilute acetic acid (charcoal) then from benzene, and finally from alcohol, giving the *compound* as very pale pinkish-yellow needles, m. p. 205°, softening at 198° (Found: C, 74·6; H, 5·3. $C_{19}H_{16}O_2N_2$ requires C, 75·0; H, 5·3%). (ii) Hot benzene solutions of 3-(β-aminoethyl)indole (0·19 g.) and o-carbomethoxyphenylacetic acid (0·3 g.) (Wegscheider and Glogau, *Sitzungsber. Akad. Wien*, 1903, **112**, 2B, 782) were mixed and, after cooling, ether was added. The precipitated salt (0·3 g., m. p. 158—160°) was collected, washed with benzene, and heated for 30 minutes at 185°. The product (0·2 g.) was as in (i).

Attempted Cyclisation of Homophthal-(β-3-*indolylethyl*)*imide*.—(i) The imide was recovered unchanged after refluxing in benzene solution with phosphoryl chloride. (ii) The imide (0·12 g.) was refluxed for 2 hours in toluene (2 c.c.) with phosphoryl chloride (0·3 c.c.). The solvent was removed under reduced pressure and the residue crystallised first from alcohol, and then from acetic acid, giving dark red crystals, m. p. 265°, of a *compound*, probably 3-chloro-2-(β-indolylethyl)-1-*iso*quinolone (XII) (Found: C, 70·1; H, 4·75. $C_{19}H_{15}ON_2Cl$ requires C, 70·7; H, 4·65%). Some unchanged imide was also recovered.

Condensation of 3-(β-*Aminoethyl*)*indole with Homophthalic Anhydride and Attempted Cyclisation of the Product*.—The base (1 g.) and anhydride (1 g.) (Dieckmann, *Ber.*, 1914, **47**, 1432) were refluxed together in dry benzene (15 c.c.) for 3 hours. Dilute sodium hydroxide was added, the benzene layer separated, and the aqueous layer extracted with ether. The aqueous layer was then acidified (concentrated hydrochloric acid) and the resulting gum was washed with water, dissolved in dilute ammonia, and the excess of ammonia removed by evaporation on the water-bath. The filtered solution was added to a solution of silver nitrate (0·8 g.) in water and the precipitated silver salt (1·45 g.) was collected, washed with water and dried in a vacuum desiccator. It was suspended in dry ether (20 c.c.) and refluxed for 12 hours with methyl iodide (5 c.c.). The ether was removed from the filtered solution and the residue refluxed for 1 hour in dry benzene with phosphoryl chloride (water-bath), the benzene distilled off (water-bath), and the residue warmed with water, then cooled and filtered. The filtrate was basified (sodium hydroxide) and the resulting precipitate collected and recrystallised twice from alcohol (charcoal), giving pale yellow needles of a *compound*, m. p. 299° (10 mg.) (Found: C, 78·2; H, 4·9. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9%). This may be (IV); it is insoluble in dilute hydrochloric acid.

3-*Formyl*-2-*benzyl*-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline*.—2-Benzyl-2 : 3 : 4 : 5-tetrahydro-β-carboline (0·5 g.) was heated with anhydrous formic acid (0·2 g.) for 4 hours at 185°. When cold, the mass was stirred with alcohol, and the resulting solid (0·45 g., m. p. 208—210°) recrystallised from alcohol, affording colourless crystals of 3-*formyl*-2-*benzyl*-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline*, m. p. 211—212° (Found: C, 78·7; H, 6·4. $C_{19}H_{18}ON_2$ requires C, 78·5; H, 6·2%).

We thank the University of Durham for the award of an I.C.I. Fellowship to one of us (G. A. S.).

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[*Received, December 31st*, 1945.]

129. *A Constitutional Synthesis of Cellobiose and Gentiobiose.*

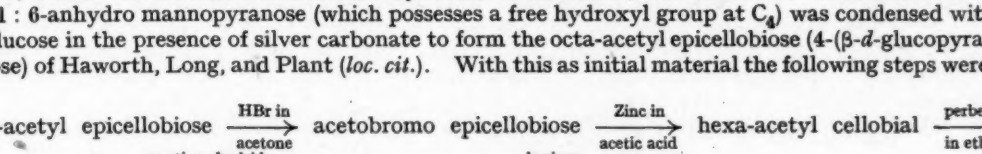
By Violet E. Gilbert, F. Smith, and M. Stacey.

The sodio derivative of 1 : 2 : 3 : 6-tetra-acetyl *β-d*-glucopyranose has been condensed in the molten state with acetobromoglucose to form directly octa-acetyl cellobiose, smoothly converted to cellobiose. Likewise 1 : 2 : 3 : 4-tetra-acetyl *β-d*-glucose was condensed with acetobromoglucose to give octa-acetyl gentiobiose and thence gentiobiose. When 3-sodio diacetone glucose was heated in a sealed tube in benzene with 6-tosyl diacetone galactose there resulted in moderate yield a *tetra-acetone disaccharide* of the true ether type. The separation of acetylated hexoses and acetylated disaccharides by chromatographic methods is described.

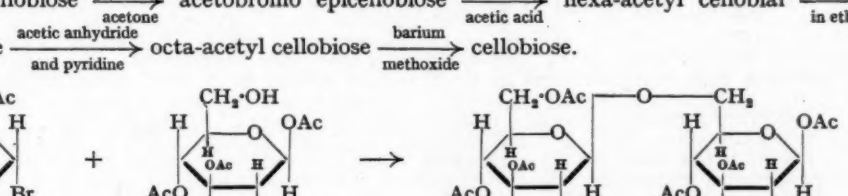
A synthesis of hepta-acetyl β-methylcellobioside in minute yield was claimed by Helferich and Bredereck (*Ber.*, 1931, **64**, 2411) who condensed acetobromoglucose with 2 : 3 : 6-triacetyl β-methylglucoside. In 1933 Freudenberg and Nagai (*Ber.*, 1933, **66**, 27) coupled 1 : 6-anhydro β-glucose with acetobromoglucose and from the syrupy reaction mixture, by means of a preferential hydrolysis to effect scission of the anhydro ring only, they obtained a product which on acetylation yielded cellobiose octa-acetate in 2% yield. This synthesis did not give any information on the structure of cellobiose because 1 : 6-anhydro β-glucose possesses three free secondary hydroxyl groups available for coupling.

Haskins, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1942, **64**, 1289) have achieved in reasonable yield an ingenious total synthesis of cellobiose by a method which, although somewhat involved, gave complete support to the structure elucidated by the classical degradative methods (Haworth, Long, and Plant, *J.*, 1927, 2809). This work, which was the first constitutional synthesis of cellobiose, was carried out as follows : 2 : 3-Monoacetone 1 : 6-anhydro mannopyranose (which possesses a free hydroxyl group at C_4) was condensed with acetobromo glucose in the presence of silver carbonate to form the octa-acetyl epicellobiose (4-(β-*d*-glucopyranosido)-*d*-mannose) of Haworth, Long, and Plant (*loc. cit.*). With this as initial material the following steps were carried out :

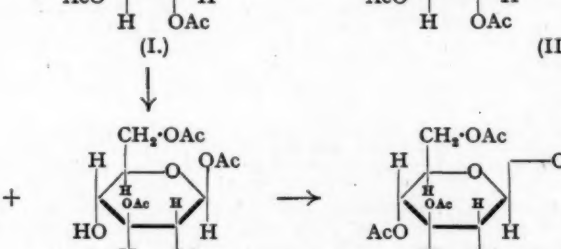
Octa-acetyl epicellobiose $\xrightarrow[\text{acetone}]{\text{HBr in}}$ acetobromo epicellobiose $\xrightarrow[\text{acetic acid}]{\text{Zinc in}}$ hexa-acetyl cellobial $\xrightarrow[\text{in ethyl acetate}]{\text{perbenzoic acid}}$ hexa-acetyl cellobiose $\xrightarrow[\text{and pyridine}]{\text{acetic anhydride}}$ octa-acetyl cellobiose $\xrightarrow[\text{methoxide}]{\text{barium}}$ cellobiose.



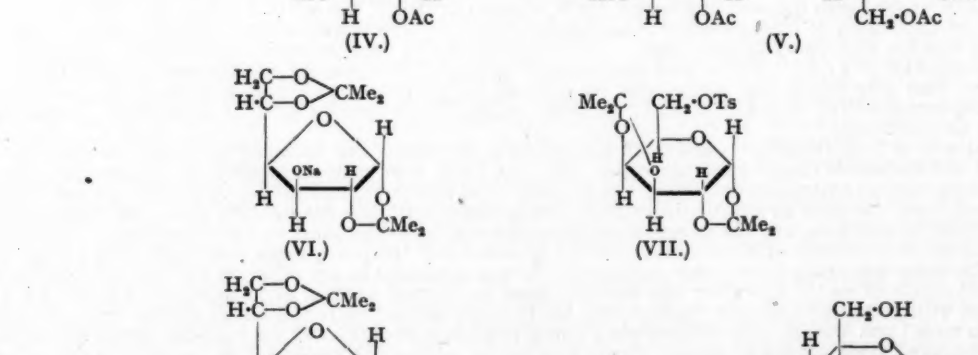
(II.) (I.) (III.)



(II) (IV.) (V.)



(VI.) (VII.)



(VIII.) (IX.)

There still appeared to be a need for a direct synthesis of cellobiose, and this achievement is now described. We discovered that some partly substituted sugars in the molten state would form sodio derivatives and, while still liquid, would react with aceto-bromohexoses with elimination of sodium bromide to form directly acetyl disaccharides.

The reaction was conveniently worked out with 1 : 2 : 3 : 4-tetra-acetyl β-*d*-glucopyranose (I) and aceto-bromoglucose (II). The former was recrystallised many times and then melted in a dry atmosphere to form a water-clear liquid in which one equivalent of dry sodium was cautiously dissolved. After addition of aceto-bromoglucose (1 mol.), and thorough mixing there was a ready separation of sodium bromide with only faint darkening of the reaction mixture. The product, extracted by chloroform, was mainly octa-acetyl gentiobiose (80% yield) (III) which was smoothly deacetylated to gentiobiose. It was noted that traces of impurity in any of the reagents rapidly caused decomposition during the reaction and the condensation mainly failed. Gentiobiose has previously been synthesised from (I) and (II) (Helferich and Klein, *Annalen*, 1926, **450**, 219) using silver oxide, or preferably silver oxide with " drierite " and iodine, as the condensing agents (Reynolds and Evans, *J. Amer. Chem. Soc.*, 1938, **60**, 2559).

For the synthesis of cellobiose, (I) was converted into 1 : 2 : 3 : 6-tetra-acetyl β-glucopyranose (IV) by the acyl migration method of Helferich and Müller (*Ber.*, 1930, **63**, 2142), and the sodio derivative of this was condensed in the molten state with (II). Since crystallisation of the disaccharide acetate was not readily achieved it was found convenient to resort to a chromatographic adsorption method of separation. For this the silica gel column of Gordon, Martin, and Synge (*Biochem. J.*, 1943, **37**, 80) was found to be eminently suitable, and using a differential solvent-extraction of the adsorbed material (including the use of a jacketed column to give elevated temperatures) it was possible, for example, to separate quantitatively 10 mg. of disaccharide acetate from 490 mg. of monosaccharide acetate.

A highly pure specimen of synthetic octa-acetyl cellobiose (V) in about 10% yield was produced from the fusion of (II) and (IV) together with approximately 30% of less pure material. The identity of the synthetic material was confirmed by comparison of its rotation, mixed melting point, and *X*-ray powder photograph with octa-acetyl cellobiose prepared from cellulose, and also by its deacetylation to authentic cellobiose.

A variation of the condensation method to give disaccharides of the true ether type has been investigated in a preliminary way. It involved the condensation of a suitable sodio derivative of a partially substituted sugar (made, for example, by the well-known method of sodio formation in liquid ammonia) with an appropriate monotosyl sugar derivative. The condensation could conveniently be carried out in a solvent at elevated temperatures in a sealed tube. 3-Sodio diacetone glucofuranose (VI) was condensed in this way with 6-tosyl diacetone galactose (VII). Sodium toluenesulphonate was separated together with unchanged diacetone glucose and diacetone galactose, and there remained a water-soluble glass having b. p. 220°/0·02 mm., $n_D^{20°}$ 1·4640. This substance was not crystallised but was considered to be a *tetra-acetone* derivative of a disaccharide having structure (VIII) for the following reasons. It had $[\alpha]_D$ −74° in chloroform whereas diacetone glucose has $[\alpha]_D$ −13° and diacetone galactose has $[\alpha]_D$ −53°. Its molecular weight was 475 (a tetra-acetone disaccharide has molecular weight 502), and it was shown to contain no free ⁻OH groups. On oxidation with nitric acid, galactosaccharic acid was formed in the expected yield, thus indicating the presence of one galactose constituent. Treatment of the tetra-acetone disaccharide with 0·5% methanolic hydrogen chloride simultaneously removed the acetone groups with loss of the furanose form of the (VI) moiety, and presumably formed the *dimethyl-glucoside* of (IX) having OMe 16·6% (theory 16·7%). Removal of the glycosidic groups with 0·25% hydrochloric acid gave (IX) as a glass having a molecular weight 340 (theory 342) and a reducing value 20% of that of glucose. The disaccharide was stable to prolonged boiling with 1% hydrochloric acid, an observation which supports the true ether type of linkage.

Experimental.

Chromatography of Mono- and Di-saccharide Acetates.—Silica gel, prepared by essentially the method of Gordon, Martin, and Synge (*loc. cit.*) but without methyl-orange treatment, was supported on a filter disc in a glass column narrowed at the base and held in a filter flask. The dimensions of the column and quantities of solvents depended upon the amount and composition of the mixture to be separated. The column was filled by suspending the gel in a 50 : 50 mixture of chloroform and light petroleum and pouring the suspension through the column under gentle suction. The liquid level was always maintained above the top of the gel. The sugar acetate mixture, dissolved in about twenty times its weight of the 1 : 1 chloroform–light petroleum solute, was drained under gentle suction (or nitrogen pressure) through the column at the rate of one drop per second.

The column was then eluted fractionally by successive extraction with small amounts of a 1 : 1 chloroform–light petroleum solute, then with chloroform alone at 20°, and finally with chloroform at 50° using a jacketed column. Each extract was worked up separately, the solvent being evaporated under reduced pressure from a weighed flask.

The separation was improved with increasing column length, but this was limited by ease of liquid flow through the gel and by the difficulty of removing the last traces of disaccharide acetate adsorbed on a large column. In those cases where partial separation only was achieved the mixed fraction could be refractionated on a fresh column.

Examples of the Separation of Artificial Mixtures.—(1) β-Glucose penta-acetate (0·05 g.) and β-cellobiose octa-acetate (0·05 g.) dissolved in a 1 : 1 chloroform–light petroleum (b. p. 40—60°) mixture (10 c.c.) were adsorbed on a column 20 cm. × 1 cm. and eluted fractionally with 10 portions (5 c.c.) of the same mixture. A complete quantitative separation was achieved, the glucose derivative being recovered in the first few extractions, and the cellobiose derivative in the remainder.

(2) β-Glucose penta-acetate (4·99 g.) and β-cellobiose octa-acetate (0·01 g.) dissolved in the 1 : 1 chloroform–light petroleum mixture (100 c.c.) were adsorbed on a column 30 cm. × 1·8 cm. The elution was carried out with five 30 c.c. fractions of the mixture, three 50 c.c. fractions of chloroform at room temperature, and two 50 c.c. fractions of chloroform

at 50°. The glucose derivative was recovered quantitatively in the first five fractions and the cellobiose derivative was extracted quantitatively by the chloroform.

(3) Using the method of example (2), β-gentiobiose octa-acetate (0·01 g.) was separated quantitatively from β-glucose penta-acetate (4·99 g.).

(4) A mixture of β-glucose penta-acetate (4 g.) and β-cellobiose octa-acetate (1·0 g.) was partially separated by the method of example (2) into β-glucose penta-acetate (2·4 g.), β-cellobiose octa-acetate (0·2 g.), and a mixture (2·4 g.) with one treatment. With two fresh columns the intermediate fractions were completely separated.

Synthesis of β-Gentiobiose Octa-acetate.—1 : 2 : 3 : 4-Tetra-acetyl β-*d*-glucose (3·5 g.), which had been repeatedly recrystallised, was put into a boiling-tube and cautiously melted in an oil-bath kept at 140°. To the colourless liquid, freshly cut sodium (0·23 g.) was added in small amounts under an atmosphere of dry nitrogen. The bath temperature was lowered to 110° and in about an hour most of the sodium had dissolved. 2 : 3 : 4 : 6-Tetra-acetyl α-glucosyl 1-bromide (4·1 g.), freshly prepared and many times recrystallised, was then added to the melt which formed a highly mobile liquid. The few residual bright globules of sodium gently dissolved and in 10—15 minutes no further visible reaction took place. The solution then gradually became opalescent owing to the separation of sodium bromide. (In the most successful reactions little or no darkening occurred, but when impure initial material was used there was extensive decomposition.) After being kept for a further hour at 110—120° the melt was cooled and extracted with chloroform (30 c.c.). The sodium bromide was thoroughly extracted with chloroform. Ether (20 c.c.) was added to the chloroform solution in order to throw out a small amount of brown tarry material and a little sodium bromide. On removal of the solvents there remained a pale yellow syrup which was dissolved in ethyl alcohol and separated into three fractions by addition of light petroleum. On being kept overnight the first two fractions crystallised (3·2 g.) and were recrystallised from alcohol–light petroleum; m. p. 190° alone or in admixture with β-gentiobiose octa-acetate, $[\alpha]_D^{20°}$ −4° in chloroform (*c*, 1·1) (Found : C, 49·6; H, 5·6; *O*-Ac, 50·3. Calc. for $C_{28}H_{38}O_{19}$: C, 49·6; H, 5·6; *O*-Ac, 50·7%). The residue from the crystallisation and the third fraction were combined (3·0 g.) and methylated, using sodium hydroxide and methyl sulphate at 30°. The product, a syrup, was distilled at 0·02 mm. giving F_I (0·5 g.), b. p. 120—130°, $n_D^{17°}$ 1·4448; F_{II} (0·5 g.), b. p. 130—180°; F_{III} (1·2 g.), b. p. 180—200°; and F_{IV}, a dark residue (0·7 g.). Fractions II—IV rapidly crystallised and after recrystallisation from light petroleum (2·1 g.) had OMe, 54·0%, $[\alpha]_D^{20°}$ −34° in water (*c*, 1·1), m. p. 106° alone or in admixture with octamethyl gentiobiose. Fraction I was shown to consist of 2 : 3 : 4 : 6-tetramethyl methylglucoside.

It was convenient after crystallising out a portion of octa-acetyl gentiobiose to acetylate the residual syrup and to separate the rest of the synthetic disaccharide acetate by fractional adsorption on a column in the manner previously described. The yields in the most successful experiments were about 80%. If the synthetic disaccharide was kept in the moist syrupy state for some days extensive decomposition with loss of acetyl residues occurred.

Octa-acetyl β-Cellobiose.—A typical synthesis was as follows. 1 : 2 : 3 : 6-Tetra-acetyl β-*d*-glucose (1·75 g.) (Helferich and Müller, *loc. cit.*) was converted mainly into the 4-sodio derivative and then fused with 2 : 3 : 4 : 6-tetra-acetyl glucosyl bromide (2·05 g.) by the method described above. (A most rigid purity was necessary for all the reactants, otherwise there was considerable decomposition and the condensation failed.) The product, a pale yellow syrup, was extracted by chloroform and the sodium bromide filtered off. The chloroform was distilled off under diminished pressure leaving a pale yellow syrup which was immediately acetylated with anhydrous sodium acetate and acetic anhydride. After removal of the acetylating reagents by distillation, the syrup was dissolved in a 1 : 1 mixture of chloroform–light petroleum and filtered from sodium acetate. It was then fractionally separated on the chromatogram in the manner described in example (4) above. There were separated penta-acetyl β-glucose (0·12 g.), various syrupy fractions, and octa-acetyl β-cellobiose (0·4 g.), m. p. 221° alone or in admixture with an authentic specimen (Found : C, 49·5; H, 5·4. Calc. for $C_{28}H_{38}O_{19}$: C, 49·6; H, 5·6%). Its identity was clearly confirmed by its *X*-ray powder photograph and by its smooth deacetylation to cellobiose, m. p. 218° alone and in admixture with a specimen from cellobiose.

Inasmuch as further small yields of the octa-acetyl β-cellobiose could be obtained after treatment of the syrupy fractions with pyridine and acetic anhydride and as low yields only of penta-acetyl glucose were obtained, it was considered that the failure of the main part of the synthetic octa-acetyl disaccharide to crystallise was due to the presence of α- and β-forms.

3-Sodio Diacetone Glucose.—Diacetone glucose (10 g.) was dissolved in liquid ammonia and treated with sodium (1 mol.; 0·88 g.). The ammonia was allowed to evaporate and the solid residue (10·85 g.) dried in a vacuum over phosphorus pentoxide and concentrated sulphuric acid.

Condensation of 3-Sodio Diacetone Glucose with 6-Tosyl Diacetone Galactose.—3-Sodio diacetone glucose from diacetone glucose (5 g.) was mixed with 6-tosyl diacetone galactose (7·9 g.) in benzene (50 c.c.). The condensation was effected by heating in a sealed tube at 100° for 12 hours and at 128° for a further 36 hours. During the first 12 hours the liquid turned brown and there was deposited an amorphous brown precipitate which increased in amount during the later heating stages but without any deepening in the colour of the liquid. The tube was cooled to 0° before it was opened. The liquid was filtered to remove the solid sodium *p*-toluenesulphonate (4·8 g.) (containing some sodium carbonate) which was washed well with acetone. The solvent was removed and the residue dissolved in a mixture of alcohol (10 c.c.) and water (80 c.c.). The solution, neutralised with carbon dioxide, was evaporated until all the alcohol was driven off and was then extracted with ether (80 c.c.). The ether extract gave a brown syrup *A* while the aqueous solution gave a syrup *B*. From *A* there was obtained by aqueous extraction diacetone glucose, m. p. 112°. The syrupy mother liquors from *A* were combined with *B* and the mixture distilled in a high vacuum giving Fraction I (5·4 g.), b. p. 155—160°/0·2 mm., $n_D^{18°}$ 1·4650, which was mainly a mixture of diacetone glucose and diacetone galactose, and Fraction II (1·1 g.), b. p. 220°/0·2 mm., $n_D^{20°}$ 1·4640. This *tetra-acetone* derivative was a hard glass-like solid insoluble in water but soluble in ether, acetone, and alcohol, $[\alpha]_D^{18°}$ −74° in chloroform (*c*, 2·0) (diacetone glucose had $[\alpha]_D^{18°}$ −14° in chloroform and diacetone galactose had $[\alpha]_D^{18°}$ −55° in chloroform). Attempts to methylate it by means of silver oxide and methyl iodide gave the initial material essentially unchanged (Found : OMe, nil.; *M* (Rast, using *K* = 47, a value found for diacetone galactose), 475. A tetra-acetone dihexose $C_{24}H_{38}O_{11}$ requires *M*, 502).

Oxidation of the Tetra-acetone Disaccharide with Nitric Acid.—The disaccharide material (120 mg.) was dissolved in nitric acid (2 c.c.; *d*, 1·2) and the solution heated at 95° for 4 hours. It was cooled and diluted with distilled water (5 c.c.). After some days a white crystalline deposit separated. This was thoroughly washed with water and the crystals were then dried (8 mg.), m. p. 220° alone or in admixture with a specimen of galactosaccharic acid (mucic acid) prepared from diacetone galactose. Under the same oxidation conditions 120 mg. of the latter yielded approximately 30 mg. of galactosaccharic acid.

Hydrolysis of the Tetra-acetone Disaccharide with Methanolic Hydrogen Chloride.—The material (0·422 g.) was boiled for 20 hours with 0·5% methanolic hydrogen chloride ($[\alpha]_D^{18°}$ −75° ⟶ + 73°) and the *dimethylglucoside* isolated in the usual manner. It was a water-soluble hygroscopic glass (0·24 g.) and was non-reducing to Fehling's solution (Found : OMe, 16·6%. $C_{14}H_{26}O_{11}$ (a dimethyl disaccharide) requires OMe, 16·7%).

Hydrolysis of the Dimethyl Disaccharide with Aqueous Hydrochloric Acid.—This material (0·16 g.) was heated for 4 hours with 0·25% aqueous hydrochloric acid ($[\alpha]_D^{18°}$ +28° ⟶ + 25°) and the product worked up as usual. It was a pale yellow water-soluble hygroscopic glass (0·06 g.), reduced Fehling's solution strongly, R.V. (Shaffer and Hartmann, *J.*

Biol. Chem., 1920, **45**, 365) 20% that of glucose, *M* (Barger's method, *J.*, 1904, **85**, 286) 340. A dihexose $C_{12}H_{22}O_{11}$ requires *M*, 342. No change could be observed in the rotation of the disaccharide after heating it with 1% aqueous hydrochloric acid for 4—5 hours.

The authors thank Professor W. N. Haworth, F.R.S., for his interest in this work, and Dr. F. J. Llewellyn for the powder photographs.

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130. *The Action of Alkaline Reagents on* 2 : 3-1 : 6- *and* 3 : 4-1 : 6-*Dianhydro* β-*Talose. A Constitutional Synthesis of Chondrosamine and Other Amino-sugar Derivatives.*

By Sybil P. James, F. Smith, M. Stacey, and L. F. Wiggins.

The action of ammonia and of sodium methoxide on 2 : 3-1 : 6- (I) and 3 : 4-1 : 6-dianhydro β-talose (II) has been investigated. With ammonia (I) gave 2-*amino* 1 : 6-*anhydro* β-*galactose*, hydrolysis with hydrochloric acid of the 1 : 6-anhydro ring of which afforded 2-amino galactose hydrochloride (identical with naturally occurring chondrosamine hydrochloride) and 3-amino 1 : 6-anhydro β-idose. The latter was also obtained by the action of ammonia from the isomeric dianhydride (II) together with 4-amino 1 : 6-anhydro β-mannose isolated as its *hydrochloride*. Both dianhydrides underwent ring scission on sodium methoxide treatment, (I) giving 2-methyl 1 : 6-anhydro β-galactose and (II) giving 4-methyl 1 : 6-anhydro β-mannose. No crystalline derivative of 3-methyl 1 : 6-anhydro β-idose, which theoretically should also have been formed, could be isolated.

A brief outline of a constitutional synthesis of chondrosamine from 2 : 3-1 : 6-dianhydro β-talose has been given (James *et al.*, *Nature*, 1945, **156**, 308). In the present paper this synthesis is described in detail and the work has been extended to include a study of the action of sodium methoxide on 1 : 6-anhydro talose derivatives.

It is now well established in the sugar series that scission of an anhydro ring of the ethylene oxide type, in which the ring does not engage a primary alcoholic group, takes place on both sides of the oxygen bridge and in each case is accompanied by Walden inversion giving rise to two isomeric sugar derivatives (Peat, *Ann. Reports*, 1939, **36**, 288). It has usually been observed that the amount of one isomer largely predominates over that of the other. Thus ring scission of 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside gives 2-methyl 4 : 6-benzylidene α-methylaltroside and 3-methyl 4 : 6-benzylidene α-methylglucoside in the ratio of 10 : 1 (Peat and Wiggins, *J.*, 1938, 1088). Frequently the secondary component is formed in such minute amounts as to make its isolation difficult and indeed only possible when it crystallises with particular ease or when its solubility properties differ widely from those of the primary product. An interesting example is the ring scission of 4 : 6-benzylidene 2 : 3-anhydro β-methyltaloside with alkaline reagents (Wiggins, *J.*, 1944, 522). With sodium methoxide there were obtained 3-methyl 4 : 6-benzylidene β-methylidoside and 2-methyl 4 : 6-benzylidene β-methylgalactoside. The latter was obtained with difficulty and only in small yields but the two products sufficed to determine the constitution of the anhydro compound. When this was treated with ammonia only 3-amino 4 : 6-benzylidene β-methyltaloside (63% yield) could be isolated, though a very small amount of the 2-amino galactose derivative may also have been formed.

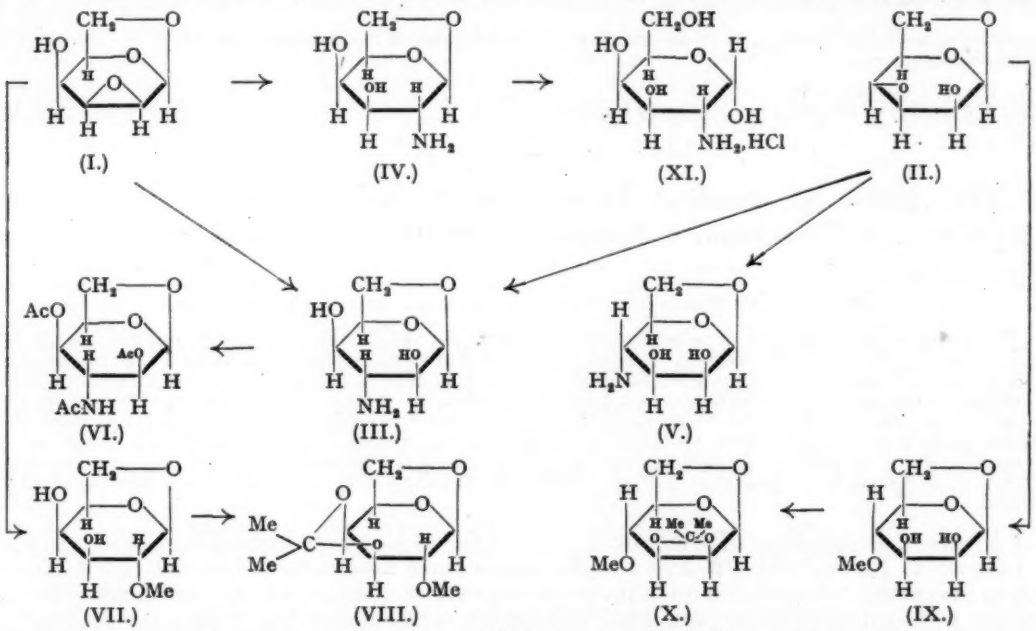
In the present work we have studied the action of both ammonia and sodium methoxide on a closely related compound in which the β-methyl glycosidic group was replaced by a β-1 : 6-anhydro ring. Here, in contrast, the 2-amino and 2-methyl derivatives predominated. We have also been able to compare the reaction of the two alkaline reagents on an isomeric dianhydride of talose (II) in which the ethylene oxide ring engages the 3 and 4 positions.

2 : 3-1 : 6-Dianhydro β-talose (I), first prepared by Hann and Hudson (*J. Amer. Chem. Soc.*, 1942, **64**, 2435) (who, however, did not provide experimental details), was obtained as follows. 3 : 4-Monoacetone 1 : 6-anhydro β-galactose was converted into 2-*methanesulphonyl* 3 : 4-*monoacetone* 1 : 6-*anhydro* β-*galactose*, mild acid hydrolysis of which gave 2-*methanesulphonyl* 1 : 6-*anhydro* β-*galactose* in good yield. The methanesulphonyl residue was readily removed by sodium methoxide at room temperature with formation of 2 : 3-1 : 6-dianhydro β-talose (I). 3 : 4-1 : 6-Dianhydro β-talose (II) was obtained by the method of Hann and Hudson (*J. Amer. Chem. Soc.*, 1942, **64**, 925).

By analogy with investigations on 2 : 3-anhydro β-methyltaloside it was expected that treatment of (I) with aqueous ammonia would give mainly 3-amino 1 : 6-anhydro β-idose (III) together with a small amount of 2-amino 1 : 6-anhydro β-galactose (IV). The results showed, however, that the action of ammonia gave (IV) (isolated as the crystalline *hydrochloride*) in 56% yield while (III) was formed in very low yield indeed and was obtained only in the form of its acetyl derivative, 3-*acetamido* 2 : 4-*diacetyl* 1 : 6-*anhydro* β-*idose* (VI).

Similarly when sodium methoxide was used to effect the scission of the 2 : 3-anhydro ring in (I), 2-methyl 1 : 6-anhydro β-galactose (VII), isolated as its *monoacetone* derivative (VIII), was obtained in 60% yield and no idose derivative could be isolated in the pure state. Thus considering the scission by alkaline reagents of the 2 : 3-anhydro ring in these talose derivatives it was clear that the β-1 : 6-anhydro ring exercised a directing influence different from that shown by the β-methyl glucosidic group; in the first case the entering anion (James *et al.*, *loc. cit.*) attaches itself mainly to C_2 and in the second case mainly to C_3 of the sugar molecule.

Clear proof of the constitutions of (III) and (IV) was obtained from a comparative study of the action of ammonia on the two isomeric dianhydrides (I) and (II). Treatment of (I) with ammonia under pressure, followed



by hydrolysis of the products with hydrochloric acid, yielded a crystalline hydrochloride, $[\alpha]_D^{22}$ −15·5°, and a residue which by acetylation gave a crystalline amino triacetyl anhydrohexose. The latter was also formed from (II) by the same reactions together with a second crystalline hydrochloride. Now on scission of the 2 : 3-anhydro ring in (I) by ammonia there should be obtained 2-amino 1 : 6-anhydro β-galactose (IV) and 3-amino 1 : 6-anhydro β-idose (III), while from (II) the ammonolysis products should be (III) and 4-amino 1 : 6-anhydro β-mannose (V). Thus the common amino triacetyl anhydrohexose above was undoubtedly a derivative of (III), *i.e.*, 3-acetamido 2 : 4-diacetyl 1 : 6-anhydro β-idose (VI), m. p. 245—246°, $[\alpha]_D^{20°}$ −71° in chloroform. The first hydrochloride was that of (IV) and the second hydrochloride was that of (V); the latter on acetylation gave 4-*acetamido* 2 : 3-*diacetyl* 1 : 6-*anhydro* β-*mannose*, m. p. 180°, $[\alpha]_D^{18°}$ −76° in chloroform, which was quite distinct from (VI).

On treatment of (II) with sodium methoxide there was obtained 4-methyl 1 : 6-anhydro β-mannose (IX) isolated as its 2 : 3-monoacetone derivative (X) in 60% yield. (IX) was identical with the substance obtained by methylation of 2 : 3-monoacetone 1 : 6-anhydro β-mannose (Hann and Hudson, *loc. cit.*). 3-Methyl 1 : 6-anhydro β-idose should also have been present in the reaction mixture, but so far it has not been identified.

The isolation and characterisation of 2-amino 1 : 6-anhydro β-galactose made possible the solution of an outstanding problem in carbohydrate chemistry, namely the precise configuration of chondrosamine, the naturally occurring amino sugar present in cartilagenous tissue. Since chondrosamine on treatment with phenylhydrazine (Levene, " Hexosamines and Mucoproteins," Longmans, Green and Co., London, 1925) gives galactosazone, it would appear to be either 2-amino galactose or 2-amino talose, a point which Levene (*loc. cit.*) demonstrated more strongly by his synthesis of chondrosamine by an " ascent of the series " from 1-amino lyxose. If in fact chondrosamine is 2-amino galactose then hydrolysis of the 1 : 6-anhydro ring in 2-amino 1 : 6-anhydro galactose (IV), a scission which must occur without any configurational change in the molecule other than on C_1, will give chondrosamine. This hydrolysis was achieved using concentrated hydrochloric acid, and 2-amino galactose hydrochloride (XI) was obtained in well-formed crystals and good yield. It showed $[\alpha]_D$ +125°→+98° in one hour, a value identical with that of a specimen of chondrosamine hydrochloride prepared from bovine tracheal cartilage (Stacey, *J.*, 1944, 272). Complete identity of the synthetic material with chondrosamine hydrochloride was established by a comparison of their *X*-ray powder photographs. Finally 2-acetamido tetra-acetyl β-galactose, m. p. 238°, prepared from the synthetic material was identical with β-penta-acetyl chondrosamine (Stacey, *loc. cit.*).

The stability of the 1 : 6-anhydro ring in (IV) is of interest. Not only were more drastic conditions needed for hydrolysis by means of aqueous acid than is usual even for the methylated derivatives of 1 : 6-anhydro β-galactose (cf. McCreath and Smith, *J.*, 1939, 347), but attempted acetolysis of (IV) failed to achieve scission of the 1 : 6-anhydro ring.

Experimental.

2-*Methanesulphonyl* 3 : 4-*Monoacetone* β-1 : 6-*Anhydro Galactose*.—3 : 4-Monoacetone β-1 : 6-anhydro galactose (4·01 g.) (Hann and Hudson, *loc. cit.*) was dissolved in anhydrous pyridine (20 c.c.) and methanesulphonyl chloride (2·4 c.c.) was added drop by drop with shaking. After being kept overnight the crystalline mass which separated was transferred into

ice-cold water and the crystals (4·6 g.) collected, washed with water, and dried in a vacuum over phosphorus pentoxide. Recrystallisation from methyl alcohol gave *2-methanesulphonyl* 3 : 4-*monoacetone* β-1 : 6-*anhydro galactose* (4·2 g.), m. p. 156°, $[\alpha]_D^{15°}$ −47° in chloroform (*c*, 1·6) (Found : C, 43·1; H, 6·0. $C_{10}H_{16}O_7S$ requires C, 42·8; H, 5·8%).

2-Methanesulphonyl β-1 : 6-*Anhydro Galactose.*—2-Methanesulphonyl 3 : 4-monoacetone β-1 : 6-anhydro galactose (6·8 g.) was boiled under reflux for seven hours with ethyl alcohol (250 c.c.) containing 0·5N-sulphuric acid (120 c.c.). After being kept overnight the solution was diluted with water and neutralised with barium carbonate. The solution was filtered and the residue washed repeatedly with hot water. The filtrate and washings were evaporated to dryness under reduced pressure and the residue extracted with boiling alcohol. Evaporation of the filtered extract gave a mass of crystals which on recrystallisation from ethyl alcohol gave *2-methanesulphonyl* β-1 : 6-*anhydro galactose* (4·2 g.), m. p. 145°, $[\alpha]_D^{14°}$ −11° in methyl alcohol (*c*, 0·9) (Found : C, 35·5; H, 4·9; S, 13·2. $C_7H_{12}O_7S$ requires C, 35·0; H, 5·0; S, 13·3%).

2 : 3-1 : 6-*Dianhydro* β-*Talose.*—2-Methanesulphonyl β-1 : 6-anhydro galactose (3·04 g.) was dissolved in dry methyl alcohol (100 c.c.) and sodium methoxide (9·3 c.c. of 1·5 N-solution) was added to the cooled solution. The course of the reaction was followed polarimetrically : $[\alpha]_D^{18°}$ −11·5° (initial value); −26° (3 hrs.); −42° (16 hrs.); −43° (18·5 hrs.); −47° (63 hrs.; constant value). The solution was neutralised (litmus) and evaporated to dryness at 40° under reduced pressure. The residue was extracted with acetone and the filtered extract evaporated to a crystalline residue (1·9 g.). This was recrystallised from acetone–ether when 2 : 3-1 : 6-dianhydro β-talose (1 g.) was obtained, m. p. 132°, $[\alpha]_D^{20°}$ −88° in water (*c*, 0·76) (Found : C, 49·9; H, 5·5. Calc. for $C_6H_8O_4$: C, 50·0; H, 5·5%).

The Ammonolysis of 2 : 3-1 : 6-*Dianhydro* β-*Talose.*—Dianhydro talose (1·3 g.) was heated with ammonia (170 c.c.; *d* 0·880) in an autoclave at 100° for 30 hours. The solution was evaporated under reduced pressure in an atmosphere of nitrogen to give a syrup which was purified by treatment with charcoal in aqueous solution. Evaporation finally gave a syrup (1·52 g.) which partly crystallised.

In a previous experiment these crystals were separated by trituration with warm ethyl alcohol and recrystallised from *iso*propyl alcohol. They were *2-amino* β-1 : 6-*anhydro galactose* and had m. p. 168—170°, $[\alpha]_D^{18°}$ −27·5° in water (*c*, 0·64) (Found : N, 8·8. $C_6H_{11}O_4N$ requires N, 8·7%).

The product was dissolved in alcohol, and N-hydrochloric acid (9·3 c.c.) added. The solution was evaporated to dryness and the solid residue recrystallised from aqueous methyl alcohol when the *hydrochloride* of 2-amino β-1 : 6-anhydro galactose (1·01 g.; 56% of the theoretical), m. p. 215° (decomp.), $[\alpha]_D^{22°}$ −15·5° in water (*c*, 2·2), was obtained (Found : C, 36·9; H, 6·1; N, 6·5; Cl, 17·6. $C_6H_{12}O_4NCl$ requires C, 36·4; H, 6·1; N, 7·1; Cl, 18·0%).

Examination of the Residual Syrup.—When all the crystalline 2-amino β-1 : 6-anhydro galactose hydrochloride had been separated the remaining syrup (0·59 g.) was dissolved in anhydrous pyridine (20 c.c.) and acetic anhydride (4 c.c.) was added. The reaction mixture was kept at room temperature for 5 days and was then poured into ice-cold water. The acetylated product was extracted with chloroform, the extract washed successively with ice-cold N-hydrochloric acid, water, sodium bicarbonate solution, and water. It was then dried ($MgSO_4$), filtered, and the solvent removed. The residue (0·61 g.) partly crystallised and the crystals (0·177 g.) were separated by trituration with alcohol. They were a mixture of 2-acetamido 3 : 4-diacetyl 1 : 6-anhydro β-galactose and 3-*acetamido* 2 : 4-*diacetyl* 1 : 6-*anhydro* β-*idose* (VI). Separation of the two was effected by fractional crystallisation from alcohol. The latter substance (30 mg.) had m. p. 246°, $[\alpha]_D^{23°}$ −70° in chloroform (*c*, 0·41) (Found : C, 50·0; H, 5·85; *O*-Ac, 44·8. $C_{13}H_{17}O_7N$ requires C, 50·2; H, 5·9; *O*-Ac, 44·9%), and the former (17 mg.) had m. p. 206° alone and in admixture with a specimen prepared by acetylation of the hydrochloride of (IV) (see below).

2-Acetamido 3 : 4-*Diacetyl* 1 : 6-*Anhydro* β-*Galactose.*—2-Amino 1 : 6-anhydro β-galactose hydrochloride (96 mg.) was dissolved in anhydrous pyridine (2 c.c.) and acetic anhydride (0·3 c.c.) was added. After keeping at room temperature for several days the solvent was distilled off under reduced pressure and the residue dissolved in chloroform. The solution was washed successively with cold dilute hydrochloric acid, sodium bicarbonate solution, and water. It was then dried ($MgSO_4$), filtered, and the solvent removed. The residue (85 mg.) was recrystallised from alcohol and was *2-acetamido* 3 : 4-*diacetyl* 1 : 6-*anhydro* β-*galactose*, m. p. 207°, $[\alpha]_D^{18°}$ −73·5° in water (*c*, 0·74), $[\alpha]_D^{22°}$ −36° in chloroform (*c*, 0·55) (Found : C, 50·0; H, 5·7; *O*-Ac, 46·1. $C_{12}H_{17}O_7N$ requires C, 50·2; H, 5·9; *O*-Ac, 44·9%).

Attempted Acetolysis of 2-*Amino* 1 : 6-*Anhydro* β-*Galactose Hydrochloride.*—The material (0·152 g.) was placed in a flask and the ice-cold acetolysis mixture (4 c.c.) (35 c.c. acetic anhydride, 15 c.c. glacial acetic acid, 1 c.c. concentrated sulphuric acid) was added. The reaction mixture was allowed to stand at room temperature for 3 days, the solution cooled in ice, diluted with water, and carefully neutralised with sodium hydroxide solution (phenolphthalein). The solution was exhaustively extracted with chloroform, and the extract washed with water and dried ($MgSO_4$). Evaporation of the filtered extract gave a syrup (0·187 g.) which crystallised spontaneously. Recrystallisation from alcohol gave crystals having m. p. 208° alone and in admixture with the product from the previous experiment, and $[\alpha]_D^{18°}$ −74·2° in water (*c*, 0·3).

Hydrochloride of 2-*Amino Galactose.*—2-Amino 1 : 6-anhydro β-galactose (0·41 g.) was dissolved in 2·2N-hydrochloric acid (28 c.c.) and the solution boiled under reflux for 30 hours. The solution, filtered with the addition of charcoal, was evaporated under reduced pressure to give a white crystalline residue (0·35 g.), $[\alpha]_D^{23°}$ +108°. The product was dissolved in aqueous methyl alcohol and acetone was added to the hot solution. Needle-like crystals immediately began to separate. These were filtered off and washed with acetone. They had $[\alpha]_D^{22°}$ +125° changing to +98° in 1 hour and were 2-amino α-galactose hydrochloride (Found : C, 33·9; H, 6·62; N, 6·7; Cl, 17·2. Calc. for $C_6H_{14}O_5NCl$: C, 33·4; H, 6·54; N, 6·34; Cl, 16·5%). The specific rotation agrees well with that given for α-chondrosamine hydrochloride by Levene (*loc. cit.*). An *X*-ray powder photograph showed the identity of the synthetic with the naturally occurring compound (Stacey, *loc. cit.*).

2-Acetamido β-*Tetra-acetyl Galactose.*—The mother liquor from which the 2-amino α-galactose hydrochloride had been separated was evaporated to a syrup (0·267 g.) which was acetylated with acetic anhydride in pyridine. The product (0·413 g.) was partly crystalline. The crystals were separated by trituration with alcohol and recrystallised from alcohol and chloroform. The crystals had m. p. 238° alone and in admixture with β-penta-acetyl chondrosamine (Stacey, *loc. cit.*).

The Action of Ammonia on 3 : 4-1 : 6-*Dianhydro* β-*Talose.*—The dianhydride (2 g.) was heated with aqueous ammonia (*d* 0·88; 200 c.c.) in an autoclave for 48 hours. A clear yellow solution was obtained which after evaporation gave a yellow syrup (2·3 g.). This, dissolved in water (2 c.c.), was treated at 0° with concentrated hydrochloric acid (2 c.c.) until just acid. On the addition of alcohol prismatic crystals (A) separated (1·79 g.). The mother liquors were evaporated to give a brown syrup (B) (0·44 g.). The crystals (A) had no distinct m. p. but decomposed at 175—180°, $[\alpha]_D^{18°}$ −100·4° in water (*c*, 4·56) (no change in 24 hours) (Found : C, 36·0; H, 5·9; N, 7·1. $C_6H_{12}O_4NCl$ requires C, 36·4; H, 6·1; N, 7·1%). They were *4-amino* β-1 : 6-*anhydro mannose hydrochloride.* Yield, 79·8% of the theoretical.

The syrup (B) (0·44 g.) was acetylated by boiling under reflux for 10 minutes with acetic anhydride (10 c.c.) and fused sodium acetate (0·5 g.). The cooled mixture was poured into ice-water, neutralised with sodium bicarbonate, and the solution extracted four times with chloroform. The extract was dried ($MgSO_4$) and evaporated. The syrupy product (0·2 g.) partly crystallised and on recrystallisation from alcohol prisms were obtained which showed $[\alpha]_D^{18°}$ −71·1° in

chloroform (*c*, 0·84) and had m. p. 245—246° alone and in admixture with 3-acetamido 2 : 4-diacetyl 1 : 6-anhydro β-idose previously isolated from the products of ammonolysis of (I). Yield, 30 mg. (0·75% of the theoretical) (Found : C, 50·0; H, 6·0%).

4-Acetamido 2 : 3-*Diacetyl* β-1 : 6-*Anhydro Mannose*.—4-Amino 1 : 6-anhydro mannose hydrochloride (0·18 g.) was refluxed for 15 minutes with acetic anhydride (3 c.c.) and fused sodium acetate (0·2 g.). The mixture was poured into ice-water, neutralised with sodium bicarbonate, and the solution extracted with chloroform. The extract was dried ($MgSO_4$), filtered, and evaporated to a syrup (0·23 g.) which rapidly crystallised on trituration with alcohol. The *compound* recrystallised from alcohol in clusters of stout needles, m. p. 180°, $[\alpha]_D^{18°}$ −76·0° in chloroform (*c*, 0·54) (Found : C, 50·2; H, 5·9; N, 5·3. $C_{12}H_{17}O_7N$ requires C, 50·2; H, 5·9; N, 4·9%).

Treatment of 2 : 3-1 : 6-*Dianhydro* β-*Talose with Sodium Methoxide*.—2 : 3-1 : 6-Dianhydro β-talose (0·76 g.) was dissolved in dry methyl alcohol (25 c.c.) containing sodium (1·2 g.) and the solution was boiled under reflux for 17 hours. The solution, which became too dark for the course of the reaction to be followed polarimetrically, was cooled and neutralised to litmus with dilute sulphuric acid. It was then filtered and evaporated to dryness under reduced pressure, and the residue taken up in methyl alcohol. Acetone and ether were added and inorganic impurities separated as a brown, flocculent precipitate leaving a clear yellow solution. This was filtered and the solvent distilled off giving a syrup (0·65 g.).

The product was dissolved in acetone (50 c.c.) and concentrated sulphuric acid (0·5 c.c.) was added. The solution was kept overnight, neutralised with anhydrous sodium carbonate, filtered, and evaporated to dryness under reduced pressure in the presence of a little barium carbonate. The residue was repeatedly extracted with ether; the extract on evaporation gave a syrup (A) (0·51 g.). Extraction of the residue with alcohol gave a syrup (B) (0·022 g.). The syrup (A) crystallised on nucleation with 2-methyl 3 : 4-monoacetone 1 : 6-anhydro β-galactose. The crystals were extracted with light petroleum and the extract evaporated. The product (0·32 g.), recrystallised from light petroleum, had m. p. 37° alone or in admixture with 2-methyl 3 : 4-monoacetone 1 : 6-anhydro β-galactose, $[\alpha]_D^{22}$ −72° in water (*c*, 1·2). The syrup (B) should contain 3-methyl 1 : 6-anhydro β-idose, but no crystalline derivative has as yet been obtained.

Methylation of 3 : 4-*Monoacetone* 1 : 6-*Anhydro* β-*Galactose*.—3 : 4-Monoacetone 1 : 6-anhydro β-galactose (1 g.) was methylated three times with methyl iodide and silver oxide. After the third methylation the product was recrystallised from light petroleum and was 2-*methyl* 3 : 4-*monoacetone* 1 : 6-*anhydro* β-*galactose* (0·71 g.), m. p. 37°, $[\alpha]_D^{18°}$ in water (*c*, 2·3) (Found : OMe, 15·0. $C_{10}H_{16}O_5$ requires OMe, 14·35%).

Action of Sodium Methoxide on 3 : 4-1 : 6-*Dianhydro* β-*Talose*.—The dianhydride (1 g.) was boiled under reflux with methyl alcohol (50 c.c.) containing sodium (0·75 g.) for 30 hours. Thereafter the solution was neutralised with N-sulphuric acid and evaporated to dryness in the presence of barium carbonate. The dry residue was extracted several times with boiling ethyl acetate and on evaporation of the extract a syrup (1·22 g.) was obtained. This was treated at room temperature with acetone (200 c.c.) containing concentrated sulphuric acid (1 c.c.) for 24 hours and then the solution was neutralised with sodium carbonate, filtered, the residue washed with acetone, and the filtrate and washings evaporated to dryness. The syrupy product was extracted with light petroleum, leaving a residue (B) (0·36 g.) which should contain 3-methyl 1 : 6-anhydro β-idose but from which no crystalline material has so far been obtained. The light petroleum solution, on evaporation gave a syrup (A) (0·8 g.) which crystallised completely. On recrystallisation from ether–light petroleum it gave crystals (0·62 g.) of 4-methyl 2 : 3-monoacetone 1 : 6-anhydro β-mannose which showed $[\alpha]_D^{20°}$ −34·4° in chloroform (*c*, 1·6) and had m. p. 53° alone and in admixture with a specimen obtained by methylation of 2 : 3-monoacetone 1 : 6-anhydro β-mannose according to Hann and Hudson (*loc. cit.*). This specimen had $[\alpha]_D^{20°}$ −33·1° in chloroform (*c*, 1·2) and m. p. 53°, in agreement with the values $[\alpha]_D$ −33·4° in chloroform and m. p. 53—54° recorded by Hann and Hudson.

The authors wish to express their thanks to Professor W. N. Haworth, F.R.S., for his interest in this work, and also to Dr. F. J. Llewellyn for *X*-ray powder photographs.

A. E. Hills Laboratories,
The University, Edgbaston, Birmingham, 15. [*Received, December 20th*, 1945.]

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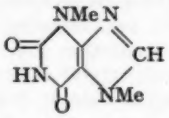
131. *An Investigation of Some Coloured Iminazolidines derived from Theobromine.*

By A. R. Todd and N. Whittaker.

The pentachloride (II) prepared by the action of chlorine on theobromine reacts with aromatic amines to give brightly coloured iminazolidine derivatives, the allophanic acid residue being eliminated. Aniline gives rise to 2-*imino*-4 : 5-*bisphenylimino*-3-*phenyl*-1-*methyliminazolidine* (V; R = Ph) and 2-*imino*-4 : 5-*bisphenylimino*-1 : 3-*diphenyliminazolidine* (VII; R = Ph) and corresponding compounds are obtained using *p*-toluidine. The structure of these compounds has been established by hydrolytic degradation and the mechanism of their formation is discussed. In the course of some synthetic experiments 4 : 5-*bisphenylimino*-2-*ketoiminazolidine* was prepared by the action of ethyl chloroformate on oxalbisphenylamidine (cyananiline).

The action of chlorine on a boiling suspension of theobromine (I) in chloroform was first studied by Fischer and Frank (*Ber.*, 1897, **30**, 2604). From the yellow solution produced in this way they isolated a colourless crystalline halogen-containing compound for which they could obtain no consistent analytical values. This difficulty in analysis they ascribed to its instability; on treatment with cold water it was converted to theobromuric acid, $C_7H_8O_5N_4$, to which they tentatively ascribed structure (III). Many years later Biltz (*Ber.*, 1934, **67**, 1856) re-examined these products and showed that the initial reaction product is to be regarded as *N*-(2 : 4 : 5 : 5-tetrachloro-1-methyl-Δ²-iminazolinyl-4)-*N*-methylallophanic acid chloride (II), and theobromuric acid as (III) in accordance with the view of Fischer and Frank; he also showed that the main reason for the unsatisfactory analytical results obtained by the latter authors lies in the fact that (II) when isolated from the reaction mixture contains 1 mol. of chloroform of crystallisation which it loses very easily. In the course of an examination of various degradations of theobromine we repeated the work of Biltz and confirmed it in all essential particulars. For the production of the pentachloride (II) trichloroethylene proved

as effective as chloroform (the product containing trichloroethylene of crystallisation) but carbon tetrachloride was unsatisfactory as a reaction medium. In an attempt to characterise (II) we treated it with ammonia but obtained only resinous products. With aromatic amines, however, (II) yielded crystalline brightly coloured products and the study of these forms the subject of this communication.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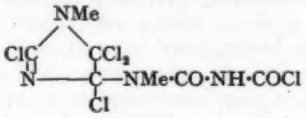
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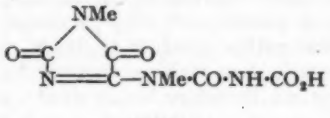
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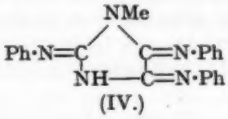
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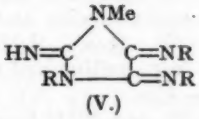
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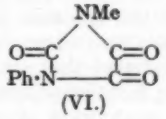
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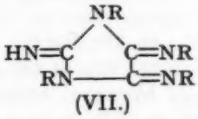
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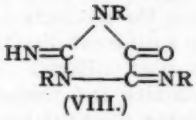
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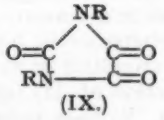

(IX.)

When a solution of aniline in benzene was added to a suspension of (II) in the same solvent, rapid reaction occurred with separation of a mixture of aniline and methylamine hydrochlorides. From the orange coloured reaction solution two yellow crystalline substances, (*A*) needles, $C_{22}H_{19}N_5$, and (*B*) plates, $C_{27-28}H_{21-23}N_5$, were isolated together with *s*-diphenylbiuret. By varying the relative proportions of the reactants and the rate of addition of the aniline it was possible to obtain either *A* or *B* in large excess. This proved to be the only really satisfactory way of preparing them in any quantity in a pure condition since similar solubilities and behaviour on chromatographic analysis made separation of mixtures of *A* and *B* in anything like equal proportions very tedious. When *p*-toluidine replaced aniline in the above reaction two yellow products, $C_{25}H_{25}N_5$ and $C_{31-32}H_{29-31}N_5$, corresponding to *A* and *B* were obtained, but when *p*-bromoaniline was used only one coloured product, $C_{22}H_{16}N_5Br_3$, corresponding to *A* was isolated.

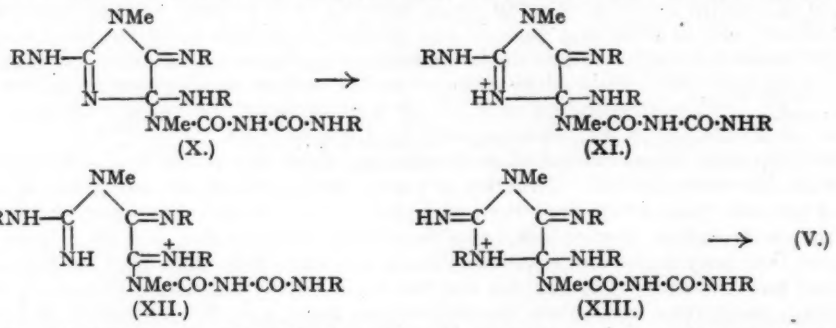
From the analytical data it was evident that *A* contained three and *B* four aryl residues together, probably, with the iminazole portion of (II). Reaction of aniline with the acid chloride grouping in (II) followed by elimination of the side chain would have been expected to yield *N*-phenyl-*N'*-methylbiuret; presumably this reacted further with aniline to give *s*-diphenylbiuret and methylamine, just as *N*-phenylbiuret reacts with aniline to give *s*-diphenylbiuret and ammonia (Schiff, *Annalen*, 1907, **352**, 78). At first sight it seemed likely that *A* would have structure (IV) but this was not borne out by the results of hydrolytic degradation. On warming *A* for a short time with dilute alcoholic hydrochloric acid the red colour of the solution was replaced by yellow, and a pale yellow product, $C_{16}H_{14}ON_4$, could be isolated. On refluxing this product or the original substance *A* with alcoholic hydrochloric acid a colourless compound, $C_{10}H_8O_3N_2$, was produced, together with ammonia and aniline. The compound $C_{10}H_8O_3N_2$ decomposed further on warming with barium hydroxide solution yielding oxalic acid and *N*-phenyl-*N'*-methylurea. It followed that the substance $C_{10}H_8O_3N_2$ must be N-*phenyl*-N'-*methylparabanic acid* (VI). Andreasch (*Ber.*; 1898, **31**, 138) claimed to have prepared this substance by desulphurising *N*-phenyl-*N'*-methyl-2-thioparabanic acid and recorded m. p. 148°, whereas our product had m. p. 210°. We therefore synthesised (VI) by condensation of phenylurea with ethyl oxalate followed by methylation; the synthetic material proved identical with that obtained from *A*. The nature of Andreasch's product remains unknown, but it evidently was not *N*-phenyl-*N'*-methylparabanic acid. The results of hydrolytic degradation make it clear that *A* is 2-*imino*-4 : 5-*bisphenylimino*-3-*phenyl*-1-*methyliminazolidine* (V; R = Ph). The yellow compound obtained by mild hydrolysis of *A* is consequently 2-imino-4- or -5-phenylimino-5- or -4-keto-3-phenyl-1-methyliminazolidine, the exact position of the keto-group being undetermined. In the same way the compounds $C_{25}H_{25}N_5$ and $C_{22}H_{16}N_5Br_3$ obtained from the reaction between (II) and *p*-toluidine and *p*-bromoaniline respectively were hydrolysed to N-p-*tolyl*-N'-*methylparabanic acid* and N-p-*bromophenyl*-N'-*methylparabanic acid*. They are therefore respectively 2-*imino*-4 : 5-*bis*-p-*tolyl*-*imino*-3-p-*tolyl*-1-*methyliminazolidine* (V; R = C_6H_4Me) and 2-*imino*-4 : 5-*bis*-p-*bromophenylimino*-3-p-*bromophenyl*-1-*methyliminazolidine* (V; R = C_6H_4Br).

There now remained the problem of the structure of *B* prepared from aniline and the pentachloride (II) and of the corresponding product from *p*-toluidine. Analytical values and molecular weight determinations by the Rast method failed to distinguish with certainty between the C_{27} and C_{28} formulæ for *B* and it was only after degradative experiments had been carried out that the formula of *B* was definitely established as $C_{27}H_{21}N_5$ and that of the *p*-toluidine product as $C_{31}H_{29}N_5$. Landgrebe (*Ber.*, 1877, **10**, 1593; 1878, **11**, 975) showed that 2 : 4 : 5-tri-imino-1 : 3-diphenyliminazolidine heated with aniline hydrochloride in alcoholic solution yields 4 : 5-di-imino-2-phenylimino-1 : 3-diphenyliminazolidine. On heating (V; R = Ph) with aniline hydrochloride in alcohol, *B* is produced in moderate yield; in analogous fashion (V; R = C_6H_4Me) can be converted by means of *p*-toluidine hydrochloride into the product $C_{31}H_{29}N_5$. That simple replacement

of the 2-imino-group had not occurred in these two cases was, however, shown when degradative experiments were carried out; as a matter of convenience these were done on the *p*-toluidine derivative.

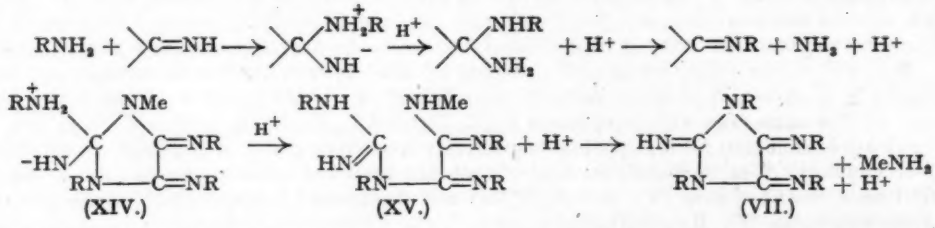
Mild hydrolysis of $C_{31}H_{29}N_5$ with aqueous hydrochloric acid gave, with elimination of one *p*-toluidine residue, a yellow compound, $C_{24}H_{22}ON_4$, while more drastic treatment with alcoholic hydrochloric acid gave a colourless substance, $C_{17}H_{14}O_3N_2$, which was evidently *NN'*-di-*p*-tolylparabanic acid (IX; R = C_6H_4Me) since it yielded *NN'*-di-*p*-tolylurea and oxalic acid on fission with alkali. Furthermore, on refluxing the original yellow product $C_{31}H_{29}N_5$ with alcoholic hydrochloric acid until the colour of the solution just disappeared, then making alkaline for a few minutes and reacidifying, *NN'*-di-*p*-tolylguanidine was isolated. There can therefore be no doubt but that the original compound is **2-*imino*-4 : 5-*bis*-p-*tolylimino*-1 : 3-*di*-p-*tolyliminazolidine*** (VII; R = C_6H_4Me), and the yellow partial hydrolysis product is **2-*imino*-4-p-*tolylimino*-5-*keto*-1 : 3-*di*-p-*tolyliminazolidine*** (VIII; R = C_6H_4Me). In accordance with this conclusion a re-examination of the reaction between *p*-toluidine hydrochloride and (V; R = C_6H_4Me) showed that methylamine hydrochloride was produced in addition to (VII; R = C_6H_4Me). By analogy with the *p*-toluidino-compound it is concluded that compound *B* prepared from aniline and the pentachloride (II) is **2-*imino*-4 : 5-*bisphenyl*-*imino*-1 : 3-*diphenyliminazolidine*** (VII; R = Ph).

The production of compounds of types (V) and (VII) from the pentachloride (II) was rather unexpected and calls for some comment. If we consider first the production of (V) it seems certain that an intermediate opening of the heterocyclic ring and re-closure in a different direction has occurred; an alternative mechanism involving the migration of an aryl group seems most unlikely. Presumably the initial step is the production of (X) by reaction of (II) with 4 mols. of arylamine and formation of 5 mols. of hydrogen chloride. It is suggested that (X) then forms a salt whose highly resonant ion may be written as (XI) or in a mesomeric form (XII) in which the tendency to change over to (XIII) by addition of the arylamino-group [located at C_2 in the initial product (X)] to C_4 is evident. (XIII) is the ion of a much weaker base than is (XI) (just as aniline is a weaker base than guanidine) and readily loses a proton from the ring nitrogen; presumably the side chain is simultaneously ejected from C_4 yielding (V) as final product of the reaction.



The formation of (VII) from (V) with elimination of methylamine as hydrochloride clearly involves a second ring-opening. A possible explanation can be given on the basis of the following normal mechanism for the acid catalysed replacement of an imino-group by an arylimino-group.

In the case of (V) the initial step would be formation of the complex (XIV). In this complex there are three other nitrogen atoms attached to the carbon atom of (V) which has been attacked by the arylamine, *i.e.*, the basicity of the molecule is not really concentrated in the NH⁻ group as represented in (XIV). Whilst any of these three nitrogen atoms might in theory receive the first proton it may be assumed that the tendency

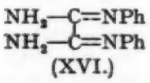


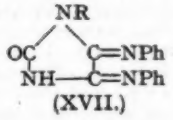
will be for it to be taken by the most nucleophilic, *i.e.*, N^1 carrying the methyl group, with a consequent opening of the labile iminazolidine ring to give (XV). Further reaction will then proceed in the direction of a stable product (VII) with loss of methylamine, ring-closure in this manner being favoured by the greater basicity of the arylamino-group as compared with the imino-group. On this view the formation of (VII) in the reaction between the pentachloride (II) and excess of arylamine in benzene solution would proceed through (V) as an intermediate. It is interesting to note that (V; R = Ph) does not react in benzene solution with aniline hydrochloride; presumably the conversion of (V) into (VII) in the original reaction of (II) with aniline occurs rapidly before protons are removed from the mixture as the insoluble aniline hydrochloride.

Arising from the above considerations it seemed that by heating (V; R = C_6H_4Me) with *m*-nitroaniline

hydrochloride it would be possible to obtain a compound analogous to (VII; R = C_6H_4Me) in which one of the cyclic nitrogen atoms bore a *m*-nitrophenyl group. In fact on refluxing an equimolecular mixture of (V; R = C_6H_4Me) and *m*-nitroaniline hydrochloride in alcohol, *p*-toluidine hydrochloride was produced together with a yellow *compound*, $C_{24}H_{22}O_2N_6$. This new product was evidently formed by replacement of a *p*-tolylimino-group at C_4 or C_5 by a *m*-nitrophenylimino-group since it yielded on hydrolysis *N*-*p*-tolyl-*N'*-methylparabanic acid. Whether the *m*-nitrophenylimino-group is attached to C_4 or C_5 remains uncertain, but it is probable that the group which it has displaced is the same as that which is readily removed from (V; R = C_6H_4Me) on mild hydrolysis. An analogous product, $C_{24}H_{23}ON_5$, was formed on heating (V; R = C_6H_4Me) with *p*-aminophenol hydrochloride in acetone; on hydrolysis it, too, yielded *N*-*p*-tolyl-*N'*-methylparabanic acid showing that the *p*-hydroxyphenylimino-residue is located at C_4 or C_5.

At an early stage in the investigation of the nature of the compound *A* from aniline and the pentachloride, it was thought possible that it might in fact be 2 : 4 : 5-trisphenylimino-1-methyliminazolidine (IV), and experiments were commenced with a view to the synthesis of this compound. Before they had been completed it was realised that our product was in fact (V; R = Ph) and as the preparation of intermediates in quantity was rather arduous the synthesis of (IV) was abandoned. Since the work actually carried out involved an iminazolidone synthesis of a new type the results obtained are recorded.


(XVI.)


(XVII.)

The route selected for the projected synthesis of (IV) was condensation of oxalbisphenylamidine (XVI) with ethyl chloroformate which by analogy with the condensation of ethyl chloroformate and malondiamidine (Howard, Lythgoe, and Todd, *J.*, 1944, 476) to 4 : 6-diamino-2-hydroxypyrimidine might yield (XVII; R = H). From (XVII; R = H) it was proposed to obtain (IV) by introduction of an anilino residue at C_2 before or after methylation of one heterocyclic nitrogen atom.

Oxalbisphenylamidine (XVI), commonly known as cyananiline after its preparation from cyanogen and aniline (Hofmann, *Annalen*, 1848, **66**, 132), has been prepared by a variety of methods; of these we found that described by Nef (*Annalen*, 1895, **287**, 282) the most convenient for preparation in quantity. On refluxing with excess of ethyl chloroformate, oxalbisphenylamidine yielded a substance, $C_{26}H_{30}O_8N_4$, presumably the *tetracarbethoxy*-derivative of oxalbisphenylamidine, while the same reaction carried out in the cold in presence of pyridine gave the *dicarbethoxy*-derivative. When equimolecular proportions of ethyl chloroformate and oxalbisphenylamidine were dissolved in pyridine and kept, the product consisted of a mixture of the dicarbethoxy-derivative and a pale yellow substance, evidently 4 : 5-*bisphenylimino*-2-*ketoiminazolidine* (XVII; R = H) since it gave on hydrolysis parabanic acid and aniline. Methylation of (XVII; R = H) with methyl iodide and methanolic sodium methoxide gave a mixture of 4 : 5-*bisphenylimino*-2-*keto*-1-*methyliminazolidine* (XVII; R = Me) and 4 : 5-*bisphenylimino*-2-*keto*-1 : 3-*dimethyliminazolidine*. (XVII; R = Me) reacted smoothly with phosphoryl chloride but the projected synthesis of (IV) was not further pursued.

Experimental.

Pentachloride (II) *from Theobromine.*—(a) *In chloroform.* Chlorine was passed through a boiling suspension of theobromine in chloroform until evolution of hydrogen chloride ceased, and the mixture worked up according to Biltz (*loc. cit.*). Yield of crystalline pentachloride, colourless plates, m. p. *ca.* 136° (decomp.), was 85%; material prepared in this way was used throughout the investigations described in this paper.

(b) *In trichloroethylene.* The procedure of Biltz (*loc. cit.*) applied to a suspension of theobromine in trichloroethylene gave a 75% yield of the pentachloride as needles, m. p. *ca.* 143° (decomp.), containing trichloroethylene. With alcohol the product gave ethyl theobromurate and with water theobromuric acid, trichloroethylene being liberated in each reaction.

Reaction of the Pentachloride (II) *with Aniline.*—(*a*) A solution of aniline (53 g. ≡ 9 mols.) in dry benzene (100 c.c.) was added within 2 minutes to a vigorously stirred suspension of the pentachloride (30 g. ≡ 1 mol.) in dry benzene (500 c.c.) at room temperature. Vigorous reaction ensued causing the benzene to reflux and the mixture became first red then orange and a white powder separated. When the reaction subsided the mixture was refluxed for 30 minutes and filtered from a mixture of aniline and methylamine hydrochloride (36 g.; theoretical, 37 g.). The filter residue was washed with warm benzene, and the combined filtrate and washings were concentrated to 150 c.c. then left overnight; a mass of colourless needles separated. These were collected and recrystallised from alcohol giving *s*-diphenylbiuret (11 g.), m. p. and mixed m. p. 208—209° (Found : C, 66·0; H, 5·2; N, 16·8. Calc. for $C_{14}H_{13}O_2N_3$: C, 65·9; H, 5·1; N, 16·5%).

Evaporation of the benzene mother liquors after removal of the *s*-diphenylbiuret gave a red resin which was dissolved in hot alcohol (150 c.c.) and the solution set aside for 3 days. The yellow needles which separated were thrice recrystallised from alcohol giving 2-*imino*-4 : 5-*bisphenylimino*-3-*phenyl*-1-*methyliminazolidine* (5·5 g.), m. p. 153—154° (Found : C, 74·8; H, 5·3; N, 20·2; *M* (Rast), 390. $C_{22}H_{19}N_5$ requires C, 74·8; H, 5·4; N, 19·8%; *M*, 353). The substance dissolved in cold alcoholic hydrochloric acid to a red solution from which it was precipitated unchanged on dilution with water. On catalytic hydrogenation using a platinum oxide catalyst it absorbed 2·8 mols. of hydrogen giving an unstable colourless product.

(*b*) When the above procedure was repeated using aniline (18 g. ≡ 11 mols.) and pentachloride (8 g. ≡ 1 mol.) the products were *s*-diphenylbiuret (2·5 g.) and 2-*imino*-4 : 5-*bisphenylimino*-1 : 3-*diphenyliminazolidine* (2·7 g.), the latter crystallising from alcohol as yellow plates, m. p. 177—178° (Found : C, 77·9; H, 5·4; N, 16·8; *M* (Rast), 422. $C_{27}H_{21}N_5$ requires C, 78·0; H, 5·1; N, 16·9%; *M*, 415. $C_{28}H_{23}N_5$ requires C, 78·3; H, 5·4; N, 16·3%; *M*, 429).

The substance dissolved in cold alcoholic hydrochloric acid to a red solution from which it was precipitated unchanged on dilution with water.

(*c*) Variation in the proportion of aniline and pentachloride between those used in (*a*) and (*b*) gave mixtures of approximately equal quantities of the two yellow compounds, as also did slower addition of the aniline solution (10 or more minutes).

Reaction of the Pentachloride (II) *with* p-*Toluidine*.—(*a*) The reaction was carried out exactly as in the case of the aniline experiment (*a*) above using *p*-toluidine (60 g. ≡ 9 mols.) and pentachloride (30 g. ≡ 1 mol.). After removal of *p*-toluidine and methylamine hydrochlorides and crystallisation of the *s*-di-*p*-tolylbiuret, the benzene solution was evaporated, and the residue stirred with water (200 c.c.) and again evaporated to remove any residual benzene and *p*-toluidine. The residue was dissolved in hot alcohol (180 c.c.) and left for 24 hours, and the crystalline precipitate was collected and recrystallised twice from alcohol. 2-*Imino*-4 : 5-*bis*-p-*tolylimino*-3-p-*tolyl*-1-*methyliminazolidine* (V; R = C_6H_4Me) was obtained in yellow hexagonal plates (6·8 g.), m. p. 169° (Found : C, 76·4; H, 6·2; N, 17·7. $C_{25}H_{25}N_5$ requires C, 76·0; H, 6·3; N, 17·7%). It closely resembled (V; R = Ph) in properties.

Water (10 c.c.) was added to the alcoholic mother liquor remaining after separation of (V; R = C_6H_4Me). After 24 hours the crystalline precipitate was collected and twice recrystallised from alcohol giving yellow needles (2·6 g.) of 2-*imino*-4 : 5-*bis*-p-*tolylimino*-1 : 3-*di*-p-*tolyliminazolidine* (VII; R = C_6H_4Me), m. p. 178—179° (Found : C, 79·0; H, 6·3; N, 14·8. $C_{31}H_{29}N_5$ requires C, 79·0; H, 6·2; N, 14·9%). The compound contained no *N*-methyl groups.

(*b*) As in (*a*) using *p*-toluidine (45 g. ≡ 10 mols.) and pentachloride (20 g. ≡ 1 mol.) the product was (VII; R = C_6H_4Me), m. p. 178—179° (7 g.); there appeared to be very little (V; R = C_6H_4Me) present.

Reaction of the Pentachloride (II) *with* p-*Bromoaniline*.—The reaction was carried out in the normal fashion using *p*-bromoaniline (55 g. ≡ 10 mols.) and pentachloride (15 g. ≡ 1 mol.) in benzene. The only coloured product isolated was 2-*imino*-4 : 5-*bis*-p-*bromophenylimino*-3-p-*bromophenyl*-1-*methyliminazolidine* (V; R = C_6H_4Br) which, thrice crystallised from glycol monoethyl ether, formed orange plates (4·2 g.), m. p. 261—262° (Found : C, 45·1; H, 2·7; N, 11·5; Br, 40·3. $C_{25}H_{16}N_5Br_3$ requires C, 44·8; H, 2·7; N, 11·8; Br, 40·7%).

Partial Hydrolysis of (V; R = Ph).—The substance (1 g.) was dissolved in a mixture of alcohol (20 c.c.) and concentrated hydrochloric acid (4 c.c.) and the solution warmed to 60° until the red colour was replaced by yellow (*ca.* 5 minutes). It was now diluted with water (60 c.c.) and cooled, and the precipitate was collected, dried, dissolved in chloroform (15 c.c. containing 1% alcohol), and chromatographed on activated alumina, the same solvent being used for developing. The product moved fairly rapidly down the column as a compact yellow band which was washed through; the eluate so obtained was evaporated, and the residue recrystallised from alcohol. Pale yellow needles, m. p. 203° (Found : C, 68·8; H, 5·3; N, 19·9. $C_{16}H_{14}ON_4$ requires C, 69·1; H, 5·0; N, 20·1%). On refluxing with alcoholic hydrochloric acid the substance rapidly formed *N*-phenyl-*N'*-methylparabanic acid, m. p. 210°.

Hydrolysed in exactly similar fashion (V; R = C_6H_4Me) gave pale yellow needles, m. p. 235° (Found : C, 70·8; H, 5·9; N, 17·8. $C_{18}H_{18}ON_4$ requires C, 70·6; H, 5·9; N, 18·3%). Refluxed with alcoholic hydrochloric acid the substance readily gave *N*-*p*-tolyl-*N'*-methylparabanic acid, m. p. 202°.

N-Phenyl-N'-methylparabanic Acid from (V; R = Ph).—The compound (0·5 g.) was dissolved in hot alcohol (20 c.c.), concentrated hydrochloric acid (2 c.c.) added, and the mixture refluxed for 20 minutes. On cooling the colourless solution plates (0·08 g.) separated, m. p. 210° (Found : C, 58·6; H, 3·9; N, 14·1. $C_{10}H_8O_2N_2$ requires C, 58·8; H, 3·9; N, 13·7%). The substance showed no depression in m. p. when mixed with synthetic *N*-phenyl-*N'*-methylparabanic acid (see below). On warming the substance (0·2 g.) with aqueous barium hydroxide (0·8 g. in 50 c.c. water) to 50° it gradually dissolved (10 minutes) and barium oxalate separated. After removal of the barium oxalate the solution was warmed to 80° and neutralised with sulphuric acid; barium sulphate was centrifuged off, and the clear solution concentrated to small bulk (8 c.c.). On cooling, *N*-phenyl-*N'*-methylurea separated in small colourless plates; recrystallised from water it had m. p. 150—151° undepressed in admixture with an authentic specimen (m. p. 150—151°).

From the hydrolysis mother liquor left after removal of *N*-phenyl-*N'*-methylparabanic acid, it was possible to isolate, after bromination, tribromoaniline (0·9 g. Calc. for 2 mols. of aniline, 0·93 g.). Ammonia was liberated from the hydrolysis liquors on making alkaline with potassium hydroxide.

N-Phenyl-N'-methylparabanic Acid.—Sodium (0·75 g.) was dissolved in absolute alcohol (30 c.c.) and the solution added to a mixture of phenylurea (4 g.) and ethyl oxalate (4·3 g.) with shaking. Soon after all had gone into solution the sodium salt of phenylparabanic acid separated as a crystalline solid; methyl iodide (4·6 g.) and absolute alcohol (20 c.c.) were added and the mixture was refluxed for 30 minutes and allowed to cool. Colourless plates (1·4 g.) of *N*-phenyl-*N'*-methylparabanic acid separated and were recrystallised from alcohol; they had m. p. 210°, undepressed in admixture with the hydrolysis product of (V; R = Ph).

N-p-Tolyl-N'-methylparabanic Acid.—Prepared in the same manner as the *N*-phenyl analogue but using *p*-tolylurea as starting material. The *acid* crystallised from alcohol in colourless plates (yield, 90%), m. p. 202° undepressed in admixture with the product, m. p. 202°, obtained by hydrolysis of (V; R = C_6H_4Me) (Found : C, 60·6; H, 5·0; N, 12·6. $C_{11}H_{10}O_2N_2$ requires C, 60·5; H, 4·6; N, 12·8%).

N-p-Tolyl-N'-methylparabanic Acid from (V; R = C_6H_4Me).—Hydrolysed in the same manner as the corresponding aniline derivative, (V; R = C_6H_4Me) (0·5 g.) gave *N*-*p*-tolyl-*N'*-methylparabanic acid (0·1 g.), m. p. and mixed m. p. 202°.

N-p-Bromophenyl-N'-methylparabanic Acid from (V; R = C_6H_4Br).—Hydrolysis was carried out with alcoholic hydrochloric acid as described for the aniline derivative. (V; R = C_6H_4Br) (0·5 g.) gave N-p-*bromophenyl*-N'-*methylparabanic acid* (0·1 g.), m. p. 255° (Found : C, 42·2; H, 2·8; N, 10·3; Br, 27·9. $C_{10}H_7O_2N_2Br$ requires C, 42·4; H, 2·5; N, 9·9; Br, 28·3%).

Conversion of (V; R = Ph) *into* (VII; R = Ph).—A mixture of (V; R = Ph) (0·5 g.), aniline hydrochloride (0·25 g.), and alcohol (10 c.c.) was refluxed for 6 hours. On cooling the red solution, yellow plates (0·2 g.) separated which, after recrystallisation from alcohol, had m. p. 177—178° undepressed in admixture with (VII; R = Ph) (m. p. 177—178°). In exactly similar fashion (VII; R = C_6H_4Me) was prepared from (V; R = C_6H_4Me) by heating with *p*-toluidine hydrochloride in alcohol; the reaction mother liquor boiled with mercuric oxide did not yield ammonia, but methylamine was evolved on treatment with potassium hydroxide. The same product was obtained by heating the reactants in absence of solvent at 160° for 10 minutes.

Partial Hydrolysis of (VII; R = C_6H_4Me).—(VII; R = C_6H_4Me) (0·5 g.) was heated under reflux for 1 hour with water (10 c.c.) and concentrated hydrochloric acid (10 c.c.). The initial red coloration faded giving place to yellow, and a yellow crystalline solid separated. The solid was collected, dissolved in chloroform containing 1% of alcohol, and purified by chromatography on activated alumina and recrystallisation from alcohol. 2-*Imino*-4-p-*tolylimino*-5-*keto*-1 : 3-*di*-p-*tolyliminazolidine* (VIII; R = C_6H_4Me) was obtained as yellow plates, m. p. 249—250° (Found : C, 75·7; H, 6·1; N, 14·3. $C_{24}H_{21}ON_4$ requires C, 75·4; H, 5·8; N, 14·7%).

NN'-Di-p-tolylparabanic Acid from (VII; R = C_6H_4Me).—The following procedure was found most satisfactory. (VII; R = C_6H_4Me) (0·5 g.) was heated with alcohol (20 c.c.) and concentrated hydrochloric acid (3 c.c.) in a sealed tube at 100° during 1 hour. Evaporation of the solution and recrystallisation of the residue from aqueous alcohol gave colourless prisms of *NN'*-di-*p*-tolylparabanic acid, m. p. 135—136°. Landgrebe (*Ber.*, 1877, **10**, 1590) gives

m. p. 144° (Found: C, 69·9; H, 4·8; N, 9·7. Calc. for $C_{17}H_{14}O_2N_2$: C, 69·5; H, 4·8; N, 9·5%). Further evidence for the identity of this product was obtained by heating it at 80° for 3 minutes with aqueous alcoholic potassium hydroxide (*ca.* 2%). The product which separated on cooling crystallised from aqueous alcohol in colourless needles, m. p. 266—267° undepressed by authentic *NN'*-di-*p*-tolylurea.

NN'-Di-p-*tolylguanidine from* (VII; R = C_6H_4Me).—A mixture of (VII; R = C_6H_4Me) (1 g.), alcohol (30 c.c.), and concentrated hydrochloric acid (4 c.c.) was refluxed for 15 minutes. The pale yellow solution was made alkaline with potassium hydroxide, boiled for 5 minutes, and then acidified to Congo-red with hydrochloric acid. The solution was now evaporated under reduced pressure, the residue extracted with water (100 c.c.), and the filtered solution made alkaline with ammonia. Fine colourless needles separated on standing; these were collected after 2 days and recrystallised several times from light petroleum (b. p. 80—100°) giving *NN'*-di-*p*-tolylguanidine, m. p. 166—167°, undepressed in admixture with an authentic specimen (m. p. 167—168°) (Found: C, 75·0; H, 6·9; N, 18·0. Calc. for $C_{15}H_{17}N_3$: C, 75·3; H, 7·1; N, 17·6%).

Reaction of (V; R = C_6H_4Me) *with* m-*Nitroaniline Hydrochloride*.—A mixture of (V; R = C_6H_4Me) (1 g.), *m*-nitroaniline hydrochloride (0·45 g.), and alcohol (25 c.c.) was refluxed for 20 minutes, cooled, and set aside. After 2 hours the yellow plates which had separated were collected and recrystallised from alcohol. The *product* (0·2 g.) had m. p. 225—227° (Found: C, 68·0; H, 5·3; N, 19·7. $C_{24}H_{22}O_2N_6$ requires C, 67·7; H, 5·2; N, 19·7%). From the neutralised mother liquors *p*-toluidine was isolated.

Reaction of (V; R = C_6H_4Me) *with* p-*Aminophenol Hydrochloride*.—A mixture of (V; R = C_6H_4Me) (0·5 g.), *p*-aminophenol hydrochloride (0·2 g.), and acetone (20 c.c.) was refluxed for 1 hour, filtered from solid hydrochlorides, and evaporated. The residue was dissolved in chloroform (20 c.c.) and chromatographed on activated alumina, the same solvent being used for developing. Unchanged starting material (0·26 g.) passed rapidly through the column leaving an orange band which was eluted with alcohol–acetone (1 : 1). Evaporation of the eluate and recrystallisation from alcohol gave the *product* as yellow needles (0·15 g.), m. p. 253—254° (Found: C, 72·0; H, 5·5; N, 17·8. $C_{24}H_{23}ON_5$ requires C, 72·5; H, 5·8; N, 17·6%). The substance was insoluble in aqueous but dissolved in alcoholic potassium hydroxide to a red solution from which it could be recovered by acidifying with hydrochloric acid and neutralising with ammonia.

Tetracarbethoxyoxalbisphenylamidine.—A mixture of oxalbisphenylamidine (2 g.) and ethyl chloroformate (6 c.c.) was refluxed for 15 minutes when the amidine dissolved and a pale yellow solid separated. Benzene (20 c.c.) was added and the precipitate of oxalbisphenylamidine hydrochloride collected and washed with benzene (10 c.c.). The combined filtrate and washings were evaporated and the residue was recrystallised from alcohol; the *tetracarbethoxy*-derivative formed colourless plates (0·6 g.), m. p. 144° (Found: C, 59·1; H, 5·7; N, 10·8; *M* (Rast), 495. $C_{34}H_{30}O_8N_4$ requires C, 59·3; H, 5·7; N, 10·7%; *M*, 526).

Dicarbethoxyoxalbisphenylamidine.—Ethyl chloroformate (5 c.c.) was added with shaking to a solution of oxalbisphenylamidine (2 g.) in dry pyridine (50 c.c.). After 3 hours the precipitated hydrochloride was filtered off and the yellow solution evaporated under reduced pressure. The residue was washed with dilute hydrochloric acid and recrystallised from alcohol; colourless needles (0·8 g.), m. p. 230—231° (Found: C, 63·1; H, 5·4; N, 14·3. $C_{30}H_{22}O_4N_4$ requires C, 62·8; H, 5·8; N, 14·7%).

4 : 5-*Bisphenylimino*-2-*ketoiminazolidine*.—Ethyl chloroformate (25 g. ≡ 1 mol.) was added during 10 minutes to a vigorously stirred suspension of oxalbisphenylamidine (55 g. ≡ 1 mol.) in dry pyridine (500 c.c.). After 3 days the red solution was filtered from precipitated hydrochloride and evaporated; the residue was extracted with dilute hydrochloric acid (4000 c.c. of N) by stirring at room temperature for several hours, and then extracted with hot alcohol (200 c.c.). The alcoholic solution yielded, on cooling, dicarbethoxyoxalbisphenylamidine (1·8 g.) while the undissolved residue, recrystallised from glycol monoethyl ether, gave pale yellow needles (2·7 g.) of 4 : 5-*bisphenylimino*-2-*ketoiminazolidine*, m. p. 284° (decomp.) (Found: C, 68·6; H, 4·5; N, 21·2. $C_{15}H_{13}ON_4$ requires C, 68·2; H, 4·6; N, 21·2%).

On refluxing the above iminazolidine (0·1 g.) with alcohol (20 c.c.) and concentrated hydrochloric acid (1 c.c.) for 10 minutes and evaporating to dryness, a residue was obtained which was then extracted with ether. The ethereal solution gave on evaporation parabanic acid, m. p. 240—241° (decomp.); mixed m. p. with authentic parabanic acid (m. p. 243°), 242°. The ether-insoluble residue consisted of aniline hydrochloride.

Methylation of 4 : 5-*Bisphenylimino*-2-*ketoiminazolidine*.—Methyl iodide (1 g.) was added to a refluxing solution of 4 : 5-bisphenylimino-2-ketoiminazolidine (0·55 g.) in methanolic sodium methoxide (4·7 c.c. of a solution made by dissolving 1 g. of sodium in 100 c.c. of methanol). After being heated for 30 minutes the solution was concentrated to half bulk and poured into water (100 c.c.). The yellow precipitate was dried, dissolved in chloroform (20 c.c. containing 1% alcohol), and chromatographed on activated alumina, the column being developed with the same solvent. Two distinct yellow bands were obtained in addition to a small amount of starting material located at the top of the column. Of these the lower, rather diffuse band, eluted with chloroform and evaporated, gave 4 : 5-*bisphenylimino*-2-*keto*-1 : 3-*dimethyliminazolidine* (0·07 g.) which crystallised from aqueous alcohol in yellow needles, m. p. 177° (Found: C, 70·2; H, 5·7; N, 19·6. $C_{17}H_{16}ON_4$ requires C, 69·9; H, 5·5; N, 19·2%).

The upper, sharply defined band was similarly eluted with chloroform and the solution evaporated. The residue, recrystallised from aqueous alcohol, gave small yellow prisms (0·15 g.) of 4 : 5-*bisphenylimino*-2-*keto*-1-*methyliminazolidine*, m. p. 183° (Found: C, 68·8; H, 5·3; N, 20·4. $C_{16}H_{14}ON_4$ requires C, 69·1; H, 5·0; N, 20·1%). A mixture with the above dimethyl compound had m. p. 151—157°.

We are grateful to the Colonial Products Research Council and to Messrs. Rowntree Ltd. for the theobromine used in this work and to the Colonial Products Research Council for a grant which enabled one of us (N. W.) to participate in the investigations. We also record our appreciation of helpful discussions of some theoretical aspects of the work with Mr. G. W. Kenner of this laboratory.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December 20th*, 1945.]

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132. *Podocarpic Acid. Synthesis of* 6- *and* 7-*Methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic Acids.*

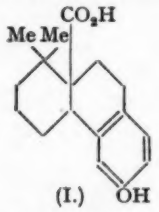
By ROBERT D. HAWORTH and BARRY P. MOORE.

6-*Methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* and the isomeric 7-*methoxy acid* have been synthesised from ethyl 2 : 6-dimethyl*cyclo*hexanone-2-carboxylate and β-(4-methoxyphenyl)ethyl bromide and β-(3-methoxyphenyl)ethyl bromide respectively by applications of the method used by Haworth and Barker (*J.*, 1939, 1299) in the synthesis of dehydroabietic acid. The constitutions of both acids have been confirmed

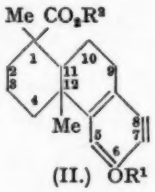
by dehydrogenation with selenium to the 6- and 7-methoxy-1-methylphenanthrenes, which have been identified by comparison with authentic specimens.

The absorption spectra of the two acids have been determined and compared with that of *O*-methylpodocarpic acid. 6-Methoxy-1 : 12-dimethyloctahydrophenanthrene-1-carboxylic acid and *O*-methylpodocarpic acid yield identical curves, and are therefore regarded as stereoisomers.

OUDEMANS (*Ber.*, 1873, **6**, 1122; *Annalen*, 1873, **170**, 214; *J. pr. Chem.*, 1874, **9**, 385) first isolated podocarpic acid, $C_{17}H_{22}O_3$, from the resin of *Podocarpus cupressinus*, and the acid was subsequently isolated (Easterfield and Aston, *Trans. New Zealand Inst.*, 1904, **36**, 483; 1910, **42**, 53; 1911, **43**, 53) from other members of the Podocarpus and Dacrydium species. Oudemans showed that podocarpic acid was a monobasic hydroxy-acid capable of nitration and sulphonation, which yielded "methanthrene," $C_{15}H_{12}$, on distillation with zinc dust, and a variety of products, including *p*-cresol, on distillation of the calcium salt. Radcliffe, Sherwood, and Short (*J.*, 1931, 2293) showed that "methanthrene" was identical with 1-methylphenanthrene, and later (*J.*, 1938, 1006) Sherwood and Short established the phenolic character of podocarpic acid and their studies on the molecular refraction of the acid indicated a tricyclic system containing three ethylenic linkages. The production of 6-methoxy-1-methylphenanthrene by dehydrogenation of the *O*-methyl ether of podocarpic acid was explained by formula (I) or (II; $R^1 = R^2 = H$) of which the former was preferred by Sherwood and Short on account of the inert character of the carboxyl group in podocarpic acid.



(I.)



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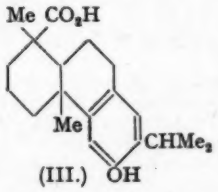
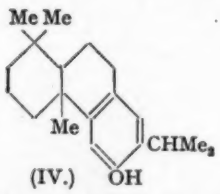


(III.)

Fieser and Campbell (*J. Amer. Chem. Soc.*, 1939, **61**, 2528) suggested that structure (II; $R^1 = R^2 = H$) had several advantages, and that 7-*iso*propylpodocarpic acid might be identical with 6-hydroxydehydroabietic acid (III). Campbell and Todd (*ibid.*, 1940, **62**, 1287) converted methyl *O*-methylpodocarpate (II; $R^1 = R^2 =$ Me) into 7-*iso*propylpodocarpic acid which differed from 6-hydroxydehydroabietic acid (III), but subsequently (*ibid.*, 1942, **64**, 928) it was shown that the two acids both yielded ferruginol (IV) when the carboxyl group was converted, *via* the aldehyde, into the methyl group. Consequently, podocarpic acid must be represented



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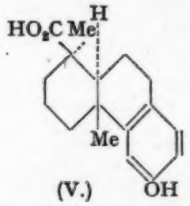
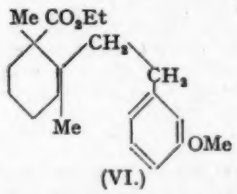


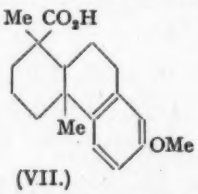
(V.)



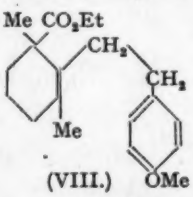
(VI.)

either by formula (II; $R^1 = R^2 = H$) or by an alternative obtained by interchanging the carboxyl and the angle methyl group. Reduction of podocarpic acid to the corresponding carbinol, followed by Wagner–Meerwein rearrangement and selenium dehydrogenation, yielded 6-methoxy-1-ethylphenanthrene. Campbell and Todd concluded therefore that podocarpic acid has structure (II; $R^1 = R^2 = H$), which conforms to the general structure of the resin acids, and they suggest that podocarpic and dehydroabietic acids both contain the *trans*-decalin structure but differ in configuration at carbon atom 1. In order to account for marked steric hindrance in podocarpic acid the configuration shown in (V) was suggested.

As a first step in the synthetical confirmation of their views, an optically inactive form of *6-methoxy-1 : 12-dimethyloctahydrophenanthrene-1-carboxylic acid* (II; $R^1 =$ Me; $R^2 = H$) has been synthesised by the reactions previously employed (Haworth and Barker, *J.*, 1939, 1299) in the synthesis of a racemic modification of dehydroabietic acid. Preliminary experiments made with β-(3-methoxyphenyl)ethylmagnesium bromide and ethyl 2 : 6-dimethyl*cyclo*hexanone-2-carboxylate yielded a carbinol, which was dehydrated by boiling with formic acid to *ethyl* 1-β-(3-*methoxyphenyl*)*ethyl*-2 : 6-*dimethyl*-Δ^6-cyclo*hexene*-2-*carboxylate* (VI). Cyclisation of this



(VII.)



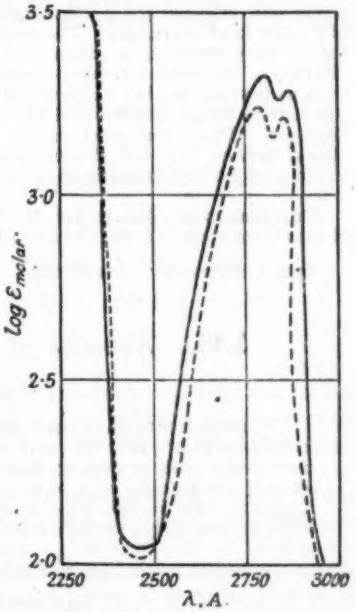
(VIII.)

*cyclo*hexene proceeded readily with acetic–sulphuric acid to give 7-*methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* (VII), m. p. 171—173°, which yielded 7-methoxy-1-methylphenanthrene on selenium

dehydrogenation, thus excluding the alternative structure with a 5-methoxyl group. The absorption spectrum (Figure) determined in methyl alcoholic solution, whilst similar to that of *O*-methylpodocarpic acid, shows sufficient displacement to justify this method of comparison as a criterion of structural identity or divergence.

The Grignard reagent from β-(4-methoxyphenyl)ethyl bromide reacted with ethyl 2 : 6-dimethyl*cyclo*hexanone-2-carboxylate to yield a carbinol which gave *ethyl* 1-β-(4-*methoxyphenyl*)*ethyl*-2 : 6-*dimethyl*-Δ^{6}-cyclo*hexene*-2-*carboxylate* (VIII) on dehydration with formic acid. Owing to the unfavourable position of the methoxyl group, cyclisation of this *cyclo*hexene derivative was expected to occasion some difficulty. This was indeed the case, and ring closure necessitated prolonged boiling with acetic–sulphuric acid. The resultant 6-*methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* (II; $R^1 = Me$; $R^2 = H$) gave 6-methoxy-1-methylphenanthrene on selenium dehydrogenation, and the absorption spectrum, determined in methyl alcoholic solution by Dr. F. B. Strauss (Oxford), was indistinguishable from that of *O*-methylpodocarpic acid under similar conditions (Figure). Demethylation of 6-methoxy-1 : 12-dimethyloctahydrophenanthrene-1-carboxylic acid proved unexpectedly difficult, and could only be effected smoothly by treatment with boiling hydriodic acid and acetic anhydride in an atmosphere of carbon dioxide. 6-*Hydroxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* (II; $R^1 = R^2 = H$), m. p. 258°, was obtained and exhibited close chemical similarity with podocarpic acid.

Resolution experiments are in progress but until these are completed it is not possible to decide whether the synthetic acid (II; $R^1 = R^2 = H$) represents racemic podocarpic acid or a diastereoisomeric modification.



—— O-*Methylpodocarpic acid and* 6-*methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid*

------ 7-*Methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid.*

Experimental.

Ethyl 1-β-(3-*methoxyphenyl*)*ethyl*-2 : 6-*dimethyl*-Δ^{6}-cyclo*hexene*-2-*carboxylate* (VI). The Grignard reagent from β-(3-methoxyphenyl)ethyl bromide (6 g.), magnesium (0·66 g.), and ether (40 c.c.) was cooled in ice, and an ice-cold solution of ethyl 2 : 6-dimethyl*cyclo*hexanone-2-carboxylate (3 g.) in ether (5 c.c.) was added during 15 minutes. The mixture, after being kept at 0° for 15 minutes and overnight at room temperature, was decomposed with ice and ammonium chloride, volatile by-products were removed, and the residue distilled. The fraction, b. p. 170—180° (oil-bath)/0·1 mm., was refluxed with anhydrous formic acid (20 c.c.) for 30 minutes, poured into water, and the product isolated with ether. The *ester* (VI) was isolated as an oil, b. p. 130—140° (oil-bath)/0·1 mm., which decolourised bromine in chloroform solution (Found: C, 76·8; H, 8·9. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·8%).

7-*Methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* (VII). Cyclisation of the above ester (VI) (2 g.) was readily effected by refluxing with glacial acetic acid (20 c.c.) and concentrated sulphuric acid (½ c.c.) for 1 hour. The mixture was poured into water, partially neutralised with sodium hydroxide, and the product isolated with ether. Removal of the ether gave an oil containing both the required acid and its ethyl ester. The mixture was hydrolysed by heating with excess of 25% alcoholic potassium hydroxide for 12 hours at 150°, poured into water, and neutral impurities removed in ether. Acidification of the alkaline layer afforded the crude acid, which was distilled in a vacuum. 7-*Methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* (VII), b. p. 170—180° (oil-bath)/0·005 mm., crystallised from aqueous methyl alcohol in colourless prisms (0·5 g.), m. p. 171—173° (Found: C, 75·4; H, 8·5. $C_{18}H_{24}O_3$ requires C, 75·0; H, 8·3%). The acid was soluble in aqueous alkali to give a crystalline sodium salt (plates from brine), and did not decolourise bromine solutions. The methoxy-acid (VII) (0·1 g.) was heated with selenium (0·125 g.) for 46 hours at 320—340°, cooled, and extracted with chloroform. The extract was distilled over sodium in a vacuum and yielded 7-methoxy-1-methylphenanthrene, m. p. 132—133°, undepressed by admixture with an authentic specimen.

Ethyl 1-β-(4-*methoxyphenyl*)*ethyl*-2 : 6-*dimethyl*-Δ^{6}-cyclo*hexene*-2-*carboxylate* (VIII). The Grignard reagent, prepared from β-(4-methoxyphenyl)ethyl bromide (9 g.) and magnesium (1 g.), in ether (30 c.c.), was condensed with ethyl 2 : 6-dimethyl*cyclo*hexanone-2-carboxylate (4·5 g.) in ether (10 c.c.) exactly as in the previous series, and the product distilled. The fraction distilling at 170—180° (oil-bath)/0·1 mm. was refluxed with anhydrous formic acid (20 c.c.) for 30 minutes, and the mixture was poured into water. The *ester* (VIII) (3 g.), isolated with ether, was obtained as an oil, b. p. 135—145° (oil-bath)/0·1 mm., which decolourised bromine in chloroform solution (Found: C, 75·7; H, 8·6. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·8%).

6-*Methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* (II; $R^1 = Me$; $R^2 = H$). The above unsaturated ester (VIII) was unaffected by stannic chloride in carbon disulphide solution. Treatment with aluminium chloride in carbon disulphide solution, followed by hydrolysis of the product with alkali under pressure, gave a small yield of the required acid. Cyclisation was best effected by refluxing the ester (VIII) (2 g.) with glacial acetic acid (12 c.c.) and concentrated sulphuric acid (½ c.c.) for 5 hours. The product was hydrolysed by heating with excess of 25% alcoholic potassium hydroxide for 12 hours at 150°, poured into water, and neutral impurities extracted with ether. Acidification of the alkaline layer afforded the crude acid, which was distilled in a vacuum. The saturated *acid* (II; $R^1 = Me$; $R^2 = H$), b. p. 190—200° (oil-bath)/0·005 mm., crystallised from ligroin (b. p. 60—80°) or aqueous methyl alcohol in colourless prisms, m. p. 194—195° (Found: C, 74·7; H, 8·4. $C_{18}H_{24}O_3$ requires C, 75·0; H, 8·3%). The acid was soluble in aqueous sodium bicarbonate solution to give a crystalline sodium salt (colourless plates from water). The *methyl* ester (II; $R^1 = R^2 = Me$), prepared in quantitative yield from the acid and diazomethane in ethereal solution, crystallised from ligroin in colourless plates, m. p. 128—129° (Found: C, 75·2; H, 8·7. $C_{19}H_{26}O_3$ requires C, 75·5; H, 8·6%). The *p-nitrobenzyl* ester, prepared from the sodium salt and *p*-nitrobenzyl bromide, crystallised from methyl alcohol in colourless plates, m. p. 128° (Found: C, 70·9; H, 7·1. $C_{25}H_{29}O_5N$ requires C, 70·9; H, 6·9%). The methoxy-acid (II; $R^1 = Me$; $R^2 = H$) (0·1 g.) was heated with selenium (0·125 g.) for 46 hours at 320—340°, cooled, and the residue extracted

with chloroform. The extract was distilled over sodium in a vacuum, and yielded 6-methoxy-1-methylphenanthrene, m. p. 85—87°, undepressed by admixture with a specimen obtained from *O*-methylpodocarpic acid.

6-Hydroxy-1 : 12-dimethyloctahydrophenanthrene-1-carboxylic acid (II; $R^1 = R^2 = H$). Demethylation of the above methoxy-acid (II; $R^1 = Me$; $R^2 = H$) (0·05 g.) was satisfactorily effected by boiling with hydriodic acid (*d* 1·7, 5 c.c.), acetic anhydride (2 c.c.), and a trace of red phosphorus for 4 hours in an atmosphere of carbon dioxide. The *product* was sublimed in a vacuum at 160—180° (oil-bath)/0·005 mm., and crystallised from aqueous acetic acid in colourless prisms, m. p. 258° (Found: C, 73·8; H, 8·1. $C_{17}H_{22}O_3$ requires C, 74·4; H, 8·0%). This acid, in alkaline solution, gave with diazotised sulphanilic acid a wine-red colouration which closely resembled that obtained with podocarpic acid.

αδ-Di-(4-methoxyphenyl)butane. (a) During the preparation of ethyl 1-*β*-(4-methoxyphenyl)ethyl-2 : 6-dimethyl-Δ^6-*cyclo*hexene-2-carboxylate (VIII), a higher fraction, b. p. 190°/0·1 mm., yielded *αδ-di-(4-methoxyphenyl)butane*, which separated from ligroin in colourless plates, m. p. 78—79° (Found: C, 79·8; H, 7·9. $C_{18}H_{22}O_2$ requires C, 79·9; H, 7·9%). Demethylation with boiling hydriodic acid (*d* 1·7) gave *αδ-di-(4-hydroxyphenyl)butane*, which separated from hot water in colourless plates, m. p. 154—155° (Found: C, 78·8; H, 7·5. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·4%), and yielded with acetic anhydride a diacetate, obtained as pearly laminæ, m. p. 88—89°, from aqueous methyl alcohol.

(b) *β*-(4-Methoxybenzoyl)propionic acid (15 g.) was refluxed with concentrated hydrochloric acid (75 c.c.) and amalgamated zinc (75 g.) for 24 hours. The mixture was cooled, extracted with ether, dried, the solvent removed, and the residual crude *β*-(4-methoxyphenyl)butyric acid (14 g.) treated with excess of freshly distilled thionyl chloride. When the vigorous reaction had subsided, the mixture was refluxed for 1 hour, excess thionyl chloride was removed, and the residue was covered with benzene and heated on the water-bath until free from benzene and thionyl chloride. The residual crude acid chloride (14 g.) was mixed with anisole (15 c.c.), nitrobenzene (25 c.c.), and powdered aluminium chloride (9 g.) and kept overnight. The complex was decomposed with ice and dilute hydrochloric acid, nitrobenzene and excess anisole were removed in steam, and the cooled residue was extracted with ether, dried, and the solvent removed. Distillation of the residue yielded *4-methoxyphenyl β-(4-methoxyphenyl)propyl ketone*, b. p. 200—210°/4 mm., which separated from methyl alcohol in colourless plates (10 g.), m. p. 92° (Found: C, 75·2; H, 6·8. $C_{18}H_{20}O_3$ requires C, 75·8; H, 7·0%). The ketone (10 g.) was reduced by heating with amalgamated zinc (50 g.) and concentrated hydrochloric acid (50 c.c.) for 12 hours. The cooled mixture was dried, and the solvent removed; the residue gave, on distillation, αδ-di-(4-methoxyphenyl)butane, b. p. 180°/2 mm., which separated from ligroin in plates (9 g.), m. p. 78—79° (Found: C, 79·9; H, 7·9%), which gave no depression in m. p. when mixed with a specimen obtained as described in (a) above.

Our thanks are due to Dr. W. F. Short for specimens of methyl *O*-methylpodocarpate and 7-methoxy-1-methylphenanthrene, and to the Department of Scientific and Industrial Research for a maintenance grant.

THE UNIVERSITY, SHEFFIELD. [*Received, January 4th*, 1946.]

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133. *Kinetics of the Halogenation of Acetone in Alkaline Solutions.*

By R. P. BELL and H. C. LONGUET-HIGGINS.

Measurements have been made of the rate of reaction of acetone with alkaline hypobromite and hypoiodite solutions at 0°, 10°, 18°, and 25°. The reaction is of zero order with respect to halogenating agent, and of first order with respect to both acetone and hydroxyl ions: hence it is concluded that the rate-determining step is the transfer of a proton from the acetone molecule to the hydroxyl ion. Comparison with other data indicates that in this type of reaction a change of substrate or catalyst is reflected primarily in a change in activation energy, though this behaviour is not common to all protolytic reactions.

ACETONE reacts with alkaline solutions of halogens according to the equation

$$CH_3{\cdot}CO{\cdot}CH_3 + 3OX^- \longrightarrow CH_3{\cdot}CO{\cdot}O^- + CHX_3 + 2OH^-.$$

It was shown by Bartlett (*J. Amer. Chem. Soc.*, 1934, **56**, 967) that with hypobromite and hypoiodite solutions containing excess of hydroxyl ions the reaction velocity is independent of the concentration of halogenating agent, and has the same value for iodine and bromine. The same behaviour is found in the base-catalysed halogenation of acetone in less alkaline solutions, where the product is tribromo- or tri-iodo-acetone. These products may well be intermediates in the haloform reaction, and in any case the rate-determining step is probably the same in the two cases, *i.e.*, the transfer of a proton from the acetone molecule to the basic catalysts present (cf., *e.g.*, Bell, "Acid-Base Catalysis," Oxford, 1941, p. 135). Bartlett records only three not very concordant experiments at 0°, and the present paper describes more extended measurements over a range of temperatures.

EXPERIMENTAL.

Most of the reactions were carried out with hypobromite solutions, which were made by adding to a solution of sodium hydroxide of known concentration an amount of bromine sufficient to convert part of it into hypobromite. (The initial concentration of hypohalite was about 0·005M in all experiments; this proved sufficient to maintain the reaction order at unity.) 2 C.c. of this solution were pipetted into each of ten tubes in the thermostat. To the first tube was added 1 c.c. of a solution of potassium iodide in N-hydrochloric acid, and the liberated iodine titrated with N/200-thiosulphate (micro-burette): this served to determine the concentration of hypobromite, and hence also that of free hydroxyl ions remaining. To each of the remaining tubes was added 1 c.c. of approximately 0·002M-acetone solution, using an automatic pipette (Bell, Lidwell, and Vaughan-Jackson, *J.*, 1936, 1794). At one-minute intervals 0·5 c.c. of potassium iodide in N-hydrochloric acid was added to successive tubes to stop the reaction and to convert the remaining hypobromite into iodine, which was titrated with N/200-thiosulphate. One tube was left for about 40 minutes and used to determine the final hypobromite concentration.

It is reasonable to suppose that the hydroxyl ion is the only effective basic catalyst present, and the results obtained confirm this. Hydroxyl ions are produced during the reaction, but in most experiments this can be allowed for with sufficient accuracy by taking the mean of the initial and final values of [OH]. In these cases the plot of $\log_{10}(x - x_\infty)$ against t (minutes) gave a straight line, where x is the thiosulphate titre at time t, and x_∞ the final titre. The catalytic constant of the hydroxyl ion, k_{OH^-}, has been previously defined (Bell and Lidwell, *Proc. Roy. Soc.*, 1940, **176**, *A*, 87)

as the rate of disappearance of halogen in moles per litre per minute in a solution which is molar with respect to both acetone and hydroxyl ions. Since three moles of halogen react with one of acetone, we have

$$k_{OH^-}[OH] = 3 \times 2{\cdot}303 \, d \log_{10} (x - x_\infty)/dt,$$

which equation was used to obtain most of the constants in Table I. In a few cases the observed value of x_∞ was checked by calculation from the known weight of acetone used in making up the solutions: there was agreement within experimental error.

The above method of calculation is applicable only when the acetone concentration is a small fraction of the hydroxyl-ion concentration. When this is not the case the correct kinetic equation is $dy/dt = k_{OH^-}(a - y)(b + 2y)$, where a and b are the initial concentrations of acetone and hydroxyl ions respectively, and $a - y$ is the acetone concentration after time t. The integrated equation is

$$(b - 2a)k_{OH^-} t = 3 \times 2{\cdot}303 \log_{10} \{a(b + 2y)/b(a - y)\}$$

and this was used to obtain the values marked with an asterisk in Table I, a, b, and y being all directly calculable from the observed titres.

The experiment marked † in the table was carried out with hypoiodite solution instead of hypobromite. In this case the plot of $\log_{10} (x - x_\infty)$ against t was a straight line for approximately the first two-thirds of the reaction, and then fell off rapidly. This is probably due to the conversion of hypoiodite into iodate (known to be rapid in alkaline solution), resulting in a hypoiodite concentration so low that it is unable to react with the acetone anions as fast as they are formed. However, this change to iodate does not render invalid the use of the thiosulphate titre as a measure of the extent of the reaction, since the conversion of hypoiodite to iodate does not affect the amount of iodine liberated in acid solution.

TABLE I.

Acetone concentration approx. 0·00077M throughout; [OH⁻] = initial concentration of hydroxyl ions.

Temp.						
25°	[OH⁻]	0·0068	0·0147	0·0153	0·0353	
	k_{OH^-}	29·0 *	31·2 †	31·8	32·6	Mean 31·2 (Calc. : 31·6)
18°	[OH⁻]	0·0119	0·0165	0·0274	0·0469	
	k_{OH^-}	18·3 *	19·1	18·7	18·7	Mean 18·7 (Calc. : 18·5)
10°	[OH⁻]	0·0122	0·0209	0·0307	0·0410	
	k_{OH^-}	8·8 *	10·8	9·7	9·3	Mean 9·6 (Calc. : 9·6)
0·07°	[OH⁻]	0·0419	0·0789	0·0819		
	k_{OH^-}	3·96	4·07	4·12		Mean 4·07 (Calc. : 4·07)

DISCUSSION.

The above results confirm Bartlett's findings (*loc. cit.*) that the reaction velocity is independent of the halogen concentration, and the same for bromine and iodine. Our value of k_{OH^-} at 0·07° (4·07) agrees well with the mean of the three values given by Bartlett for 0° (4·38, 3·93, 3·72). It should be possible to compare our value of k_{OH^-} at 25° (31·2) with values derived from measurements in buffer solutions. However, the latter values are unreliable, since in buffer solutions only a small fraction of the observed velocity is due to hydroxyl-ion catalysis, and the calculation of the hydroxyl-ion concentration is subject to uncertainties in the values to be assigned to dissociation constants and activity coefficients. The only data at all suitable are those of Dawson and Key (*J.*, 1928, 543) on phosphate buffers, and of Bell and Lidwell (*loc. cit.*, p. 88) on trichlorophenoxide buffers. Dawson and Key give $k_{OH^-} = 26$, but a recalculation of their results using more recent data on phosphate buffers gives $k_{OH^-} = 17$. Bell and Lidwell derived $k_{OH^-} = 15$, using the pH values of the trichlorophenoxide buffers observed with a glass electrode. However, measurements with a hydrogen electrode (Ogston, *J.*, 1936, 1713) give $3{\cdot}2 \times 10^{-6}$ as the dissociation constant of trichlorophenol, and using this value the same data give $k_{OH^-} = 34$. Moreover, the measurements with trichlorophenol are subject to some uncertainty because trichlorophenol itself reacts slowly with iodine, and a correction has to be applied to allow for this reaction. Our measurements in alkaline solutions thus give a value of k_{OH^-} which is of the same order of magnitude as values derived from buffer solutions, but is much more reliable.

The calculated values of k_{OH^-} in Table I are derived from the equation

$$k_{OH^-} = 2{\cdot}09 \times 10^{11} \exp. (-13{,}400/RT),$$

and it is seen that the Arrhenius equation $k = Ae^{-E/RT}$ is closely obeyed. It is of interest to compare the values of A and E with those found for the halogenation of acetone and of ethyl acetoacetate, catalysed by acetate ions (data from Smith, *J.*, 1934, 1744; Pedersen, *J. Physical Chem.*, 1934, **38**, 501). The best comparison is in terms of the ionisation velocity k', and in deriving k' from the halogenation velocities it must be remembered that the initial ionisation is followed by the rapid introduction of three and two halogen atoms for acetone and ethyl acetoacetate respectively. The comparable ionisation velocities are therefore obtained by dividing the halogenation velocities by 3 and by 2 respectively. The results are given in Table II.

TABLE II.

Constants of the Arrhenius equation.

Catalyst.	Substrate.	k' (25°).	E.	$A \times 10^{-11}$.
OH^-	Acetone	10·4	13,400	0·7
$CH_3 \cdot CO \cdot O^-$	Acetone	$2{\cdot}4 \times 10^{-4}$	22,800	1·3
$CH_3 \cdot CO \cdot O^-$	Ethyl acetoacetate	29	13,400	1·7

The variations in A are probably within experimental error, and certainly the major part of the effect of changing the catalyst or the substrate appears in the activation energy rather than in the factor A.

The same kind of behaviour had been previously found for changes of catalyst in the anion-catalysed decomposition of nitramide (Baughan and Bell, *Proc. Roy. Soc.*, **1937**, **158**, *A*, 464): on the other hand, Smith found in the acid-catalysed iodination of acetone (*loc. cit.*) and the base-catalysed mutarotation of glucose (Smith and Smith, *J.*, **1937**, 1413) that changes of catalyst were reflected in the factor A rather than in the activation energy. It is difficult to estimate the accuracy of Smith's conclusions, since most of his temperature coefficients were derived indirectly from composite velocity constants at two temperatures only. However, it is unlikely that either type of simple behaviour will apply to protolytic reactions in general, since it is well known that in a series of acid–base equilibria, changes in equilibrium constant cannot be correlated with either energy changes or entropy changes taken separately (cf. Everett and Wynne-Jones, *Trans. Faraday Soc.*, **1939**, **35**, 1380). These equilibria involve two opposed protolytic reactions, and any simple correlation between the reaction velocity and either A or E must fail for at least one of these reactions.

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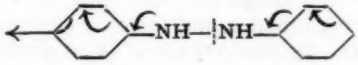
134. *Stereochemistry of the Benzidine Transformation.*

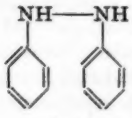
By D. LL. HAMMICK and S. F. MASON.

The benzidine transformation consists essentially in the rupture of the hydrazo, NH–NH, linkage, and the setting up of *p*–*p*′ (or *p*–*o*′, etc.) bonds. The transformation is known to be intramolecular (Ingold and Kidd, *J.*, **1933**, 984), and the two fragments must therefore be restrained from separating during the transition. Mechanisms hitherto proposed for the transformation have not dealt adequately with these forces. It has been postulated (Robinson, *J.*, 1941, 220) that partial *p*–*p*′ bonding takes place before the complete fission of the hydrazo link. The object of this paper is to examine the stereochemical limitation placed on existing theories by this postulate and to suggest structures that may contribute to an activated intermediate free from stereochemical objections.

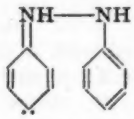
RECENTLY (*J.*, 1941, 608), Hughes and Ingold have examined the possible structures resonating in the transition complex formed during the benzidine transformation, postulating the electromeric shifts indicated below:



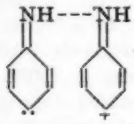
They assume heterolysis of the NH–NH link under the influence of nearby hydrogen ions, concurrent with polarisation of the *para* positions, leading to bond formation between them and the bonding of one or more protons to the nitrogen atoms. Stereochemically this cannot be a continuous process since structures arising from the above electronic displacements do not permit the approach of the *para* carbon atoms to within bond distances.



(I.)



(II.)



(III.)

Thus in structures (I), (II), and (III) the distances between the *para* carbon atoms, calculated from the known bond lengths and angles, are 4·26, 5·51, and 6·76 A. respectively.* Structure (III) is of course hypothetical, but taken as the relative position of the two fragments in space immediately after the heterolysis of the NH–NH link, it is seen that the *para* positions are separated by a distance some four times the length of a single C–C link. Heterolysis of the NH–NH link in any of the structures or hybrid of them would therefore give two fragments with the *para* positions separated by 4 A. at least, a fact difficult to reconcile with the undoubted intramolecular nature of the process, assuming continuous transition essential for such reactions.

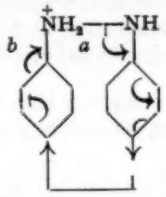
Robinson (*J.*, 1941, 220) takes into account the hydrogen ion catalysis of the reaction by proposing the

* The data in this, and following calculations, have been taken from Wells, "Structural Inorganic Chemistry" (1945). All bond angles have been assumed to be tetrahedral except in the carbonium ions which have been taken as planar (Bartlett, *J. Amer. Chem. Soc.*, **1939**, **61**, 3184). In the bonds to nitrogen this is justified as the bond angles in ammonia are 108° (Wells, *loc. cit.*); moreover the nitrogen atoms in many of these structures are quadricovalent. The bond lengths used in the calculations are as follows:

Single C–C bond, 1·54 A.	Single N–C bond, 1·46 A.
Double C=C bond, 1·33 A.	Double N=C bond, 1·27 A.
Benzene C–C bond, 1·39 A.	Single N–N bond, 1·48 A.

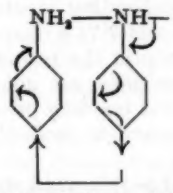
From these data the various *p*–*p*′, *o*–*p*′, and *p*–*o*′ separations were calculated trigonometrically. It should be noted that no attempt has been made to represent actual angles in the structures given.

formation of the hydrazobenzene mono-cation as the first step in the transformation. The charged centre then initiates the following electron shifts :

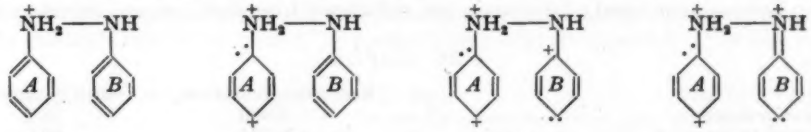


One difficulty in this mechanism, as was pointed out by Hughes and Ingold (*loc. cit.*) lies in the proposed electron recession from a positively charged centre (shift *a*). Process (*b*) moreover could not proceed to any appreciable extent as this would make the nitrogen atom quinquecovalent. Robinson avoids these difficulties by postulating a partial reversal of the electron shifts leaving the NH_2–NH bond weakened and the *para* positions partially bonded. The problem of the stereochemical feasibility of this *para* linking is recognised but left unsolved, however.

The above criticisms of the electron shifts do not arise if the electromeric effects are postulated as below :



The various structures that might be formed from these shifts are as follows :

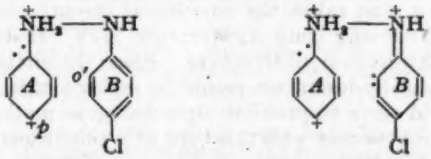


(IV.) (V.) (VI.) (VII.)

The distance between the *para* carbon atoms in structure (IV) is found to be 4·26 A. In structure (V) the minimum distance between these two atoms would be 1·50 A. as the charged nitrogen atom is no longer in the plane of the attached benzene ring; *para* bonding would therefore be stereochemically possible in this structure, the single C–C bond distance being 1·54 A. This structure, by itself, cannot represent the activated transition state because it indicates none of the polarisation effects in ring *B* that would be set up by the highly polar ring *A*, leading to *para* bonding. In structures (VI) and (VII), where the minimum *para* separations would be 1·68 A. and 2·71 A. respectively, the ring *B* *para* positions possess this polarity. Structure (VI) however possesses a positively charged carbon atom linked to a nitrogen atom with an unshared pair of electrons. We should therefore expect structure (VII), with an extra bond between these two atoms, to play a more significant rôle in the transition hybrid, were it not for the fact that it contravenes the Pauling adjacent charge rule. This rule, however, only applies to normal molecules (but is clearly contravened by hydrazine dihydrofluoride), whereas structure (VII) would represent a highly activated state with a weakened NH–NH bond.

The process of the transformation may then be pictured as the bonding of a proton to a nitrogen atom, followed by the above electromeric shifts consequent upon the setting up of the resultant charged centre. The contribution of structure (VII), and perhaps (VI), would determine the extent of *para* bonding if this were rendered stereochemically possible by structure (V) playing a major rôle in the resonance hybrid. This means that the resonance energy of ring *A* would be largely destroyed, some 39 kg.-cals./mol. being required for this purpose. This, and the 23·6 kg.-cals./mol. required for the rupture of the NH–NH link, might be provided in part by the simultaneous formation of the *p*–*p*′ C–C bond (giving 58·6 kg.-cals./mol.), so that the energy of activation need not be high by this mechanism.

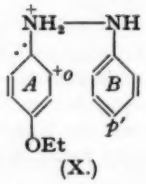
The transformation is completed by the covalent bonding of a proton to the nitrogen atom of the ring *B*, and the elimination of the *p*-hydrogen atoms as hydrogen ions. In mono-*p*-substituted hydrazobenzenes the benzidine transformation only occurs when the *p*-substituent can be eliminated as a positive ion (CO_2H, SO_3H). Where the *p*-substituent cannot be eliminated as a positive ion, two possible changes can occur. If the substituent lowers the basicity of the ring *B*, a proton will be initially bonded to the other ring, *A*. The relevant structures that might arise from the consequent electron shifts are :



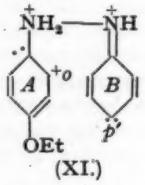
(VIII.) (IX.)

The distances between the *p*–*o*′ positions in the structures (VIII) and (IX) are 1·51 A., so that partial bonding is stereochemically possible between these positions, and would lead to the formation of a diphenyline. These compounds are in fact formed by the rearrangement of *p*-Cl, *p*-Br, *p*-I, *p*-OAc, and *p*-NMe_2 hydrazobenzenes, all these substituents lowering the basicity of a *p*-amino group under the conditions of the benzidine transformation (acid medium).

If the substituent enhances the basicity of the ring to which it is attached, *i.e.*, EtO and MeO, a proton will be bonded to the *p*-nitrogen atom. The following structures may then take part in the transition state :



(X.)



(XI.)

Here the distances between the *o*–*p*′ positions are 3·74 A. in structure (X), and 3·70 A. in structure (XI). These distances are much larger than the corresponding separations in the preceding case (both 1·51 A.) and in the benzidine transformation proper (1·50 A. and 2·71 A. respectively); in fact semidines only are produced.

The absence of an *o*-benzidine transformation in the benzene series, and the small yields of diphenylines obtained from hydrazobenzenes with free *p*-positions, are not likely to be due to steric effects, as the *o*–*o*′, and the *p*–*o*′ positions are near enough for partial bonding prior to the NH–NH link fission (but not the *o*–*p*′ positions as has already been noted). The reason is probably to be sought more in the energy content of structures formed during reaction.

It is well known that non-resonating forms of *p*-quinonoid structures are more stable than the corresponding *o*-quinonoid forms. A rough measure of this difference in stability is given by the free energy changes in the hydrogenation of *p*-benzoquinone and *o*-benzoquinone, calculated from their respective reduction potentials.

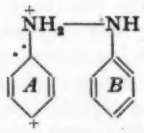
$$-\Delta G = nFE^{\circ}.$$

	Reduction potential, v.	$-\Delta G^{25°}_{aq}$, kg.-cals.
p-Benzoquinone (a)	0·699	32·2
o-Benzoquinone (a)	0·794	36·6
α-Naphthaquinone (b)	0·470	21·65
β-Naphthaquinone (c)	0·555	25·5

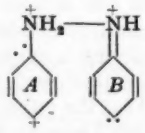
(a) Fieser and Peter, *J. Amer. Chem. Soc.*, 1931, **53**, 793. (b) La Mer and Baker, *ibid.*, 1922, **44**, 1954. (c) Fieser and Fieser, *ibid.*, 1934, **56**, 1565.

If these values of $-\Delta G^{25°}_{aq}$ are taken as rough estimates of the relative stability of the *o*-quinonoid and *p*-quinonoid configurations of the benzene ring, it is seen that some 4·6 kg.-cals. would be necessary to convert a benzenoid to an *o*-quinonoid structure, above that energy necessary to convert a benzenoid to a *p*-quinonoid structure. This only applies to "fixed" *ortho* and *para* quinonoid structures; where they are canonical structures in a resonance hybrid, their contributions are presumably slightly different, but not sufficiently to affect the stability of the hybrid to a great extent unless they play the major rôle in such a hybrid.

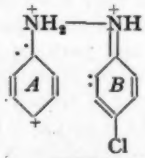
In the activated hybrid postulated, ring *A* (structure XII) has largely lost its resonance, whilst ring *B* retains it, there being a polar modification symbolised in structure (XIII).



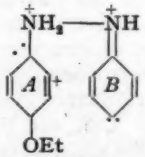
(XII.)



(XIII.)



(XIV.)

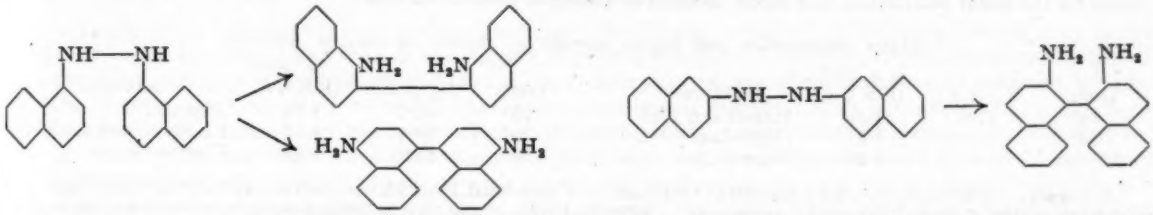


(XV.)

Where there is a *p*-substituent that reduces the basicity of the attached ring (ring *B*, structure XIV), the reaction-initiating proton is covalently linked to the nitrogen atom of the other ring (*A*) which becomes structurally *p*-quinonoid. It is postulated that resonance is largely retained in ring *B*, so the assumption of an *o*-quinonoid polarity in this ring would entail no significantly greater amount of energy than the assumption of a *p*-quinonoid polarity. Hence diphenyline formation is energetically, as well as stereochemically, feasible.

Where there is a *p*-substituent that raises the basicity of the attached ring, proton bonding takes place on the *p*-nitrogen atom of the same ring (ring *A*, structure XV). If diphenyline formation were to occur, this ring would have to assume an *o*-quinonoid structure. Since the virtual absence of resonance is postulated in this ring, the energy required for its formation would be higher; this, coupled with the greater separation of the *o*–*p*′ reactive centres, would seem to prohibit diphenyline formation, in accordance with the fact that only semidines result from hydrazobenzenes with this type of *p*-substituent.

Hydrazonaphthalenes on undergoing the benzidine transformation may yield 4 : 4′-diaminodinaphthyls, 2 : 2′-diaminodinaphthyls, or the dibenzcarbazoles produced by the elimination of ammonia from the latter; 2 : 4′-derivatives, analogues of the diphenylines, are not produced, *e.g.*:



The prevalence of an *o*-benzidine type of transformation in the naphthalene series would indicate that β-naphthaquinonoid structures are more stable than *o*-benzoquinonoid, relative to the α-naphthaquinonoid and the *p*-quinonoid structures respectively.

This is demonstrated, in part, by the differences in the free energies of hydrogenation (see Table); between α- and β-naphthaquinones it is 3·85 kg.-cals./mol. as opposed to 4·4 kg.-cals./mol. between the *o*- and *p*-benzoquinones. This would be due to the conjugation of the 3 : 4 double bond in β-naphthaquinone with the remaining benzene ring, whilst the corresponding 3 : 4 double bond in *o*-benzoquinone is only conjugated with the 5 : 6 double bond.

Another factor of importance is the degree of double bond character in the α–β link of naphthalene. Resonance amongst the three canonical structures of naphthalene gives this link 2/3 double bond character, so that α-substituents influence the β-position to a greater extent than they influence the corresponding *ortho* position in benzene. Likewise β-substituents influence position 1 to a greater extent than position 3.

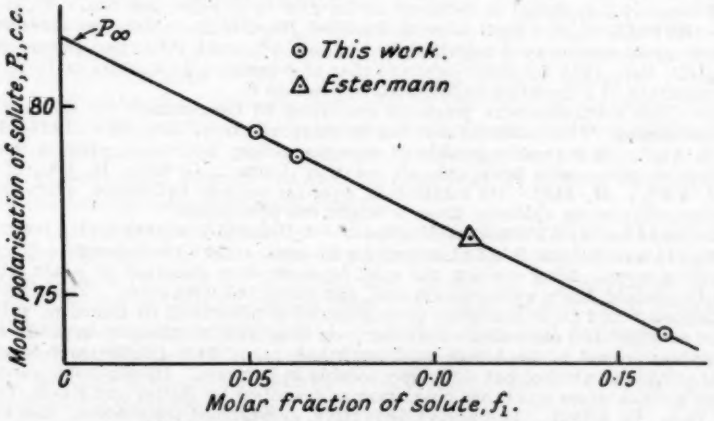
The occurrence of an *o*-benzidine type of transformation in hydrazonaphthalenes may thus be ascribed to two factors, the relative stability of " fixed " β-naphthaquinonoid structures and the ease of α-β polarisation in naphthalene.

THE DYSON PERRINS LABORATORY, UNIVERSITY OF OXFORD. [*Received, November 9th*, 1945.]

NOTES.

The Molar Polarisation of Solutions of Aniline in Benzene. By H. G. EMBLEM and C. A. MCDOWELL.

THE molar polarisation of solutions of aniline in benzene has been measured by Estermann (*Z. physikal. Chem.*, 1928, *B*, **1**, 134), Höjendahl (*Physikal. Z.*, 1929, **30**, 319), Hassel and Uhl (*Z. physikal. Chem.*, 1929, *B*, **8**, 187), Tiganik (*ibid.*, 1931, *B*, **14**, 135), and Le Fèvre and Le Fèvre (J., 1936, 1135), but there are slight discrepancies between the results. Hassel and Uhl, and Le Fèvre and Le Fèvre, report a slight increase of the molar polarisation with dilution, whereas Tiganik's measurements show practically no dependence on concentration. Estermann's work cannot be compared with these as he only measured the temperature variation of the molar polarisation of a single solution. We had occasion to measure



Molar polarisation of aniline in benzene at 20°.

accurately the polarisation of solutions of aniline in benzene and our results show a fairly definite increase in the molar polarisation with dilution. In the figure we have plotted the values for the molar polarisation of aniline in benzene solution at 20° against the molar concentration of the solution and have included the value obtained by Estermann at the same temperature; it will be seen that this is in good agreement with our results. The value of the molar polarisation at infinite dilution (P_∞ = 81·91 c.c.), calculated from our measurements by the method of least squares, is in excellent agreement with the value (P_∞ = 81·6 c.c.) obtained by Hassel and Uhl, and is slightly higher than other recorded values. From this value of P_∞, we have computed the dipole moment of aniline after allowing for the atomic polarisation,

P_A, in the manner suggested by Sugden and Groves (J., 1937, 1779, 1782), who showed that the atomic polarisation of aniline is approximately 5% of the electronic polarisation P_E; since P_E is 30·66 c.c., we get $P_{E+A} = 32·2$ c.c., and as $P_\infty = P_A + P_E + P_O$, we find P_O, the orientation polarisation, to be 49·7 c.c., yielding for the dipole moment of aniline in benzene solution at 20°, the value $1·54 \times 10^{-18}$ E.S.U. In the following table we summarize the various published values for the molar polarisation and dipole moment of aniline in benzene solution.

Molar polarisation and dipole moment of aniline in benzene solution.

Temp.	P_∞ (c.c.).	$\mu \times 10^{18}$ (E.S.U.).	Authors.	Temp.	P_∞ (c.c.).	$\mu \times 10^{18}$ (E.S.U.).	Authors.
18°	81·6	1·55	Hassel and Uhl.	20°	79·7	1·52	Tiganik.
20	—	1·51	Höjendahl.	25	78·4	1·51	Le Fèvre and Le Fèvre.
20—50	—	1·60	Estermann.	20	81·91	1·54	This work.

Apparatus.—The capacities were measured by means of a Muirhead Type 3A heterodyne capacity set which had been calibrated at the National Physical Laboratory. Calibrated cells of the Sayce–Briscoe pattern as modified by Sugden (J., 1933, 770) were employed. All measurements were made with the dielectric cell in an oil thermostat.

Calculation of Molar Polarisations.—The dielectric constants of the solutions were calculated from their measured capacities by Miller's method (*J. Amer. Chem. Soc.*, 1942, **64**, 117), and the molar polarisations of the aniline from the usual mixture formula.

Densities.—The densities of the solutions were determined in double capillary-necked pycnometers of a special design. All measurements were made in a thermostat controlled to 0·01°.

Materials.—Aniline. A sample of "AnalaR" aniline was carefully purified by Knowles's procedure (*Ind. Eng. Chem.*, 1920, **12**, 881), and then distilled several times in a vacuum; the final product had $n_D^{20°}$ 1·5860, $d_4^{20°}$ 1·0214.

Benzene. "AnalaR" Benzene was washed with concentrated sulphuric acid, dried over sodium, distilled, and frozen three times to remove homologues. A sample was refluxed over phosphoric oxide for 10 hours, stored over this reagent, and distilled from it immediately before use. The final product had $n_D^{20·5°}$ 1·5006.

Results.—In the following table, ϵ = dielectric constant, f_1 = molar fraction of aniline, $d_4^{20°}$ = density of solution, P_1 = molar polarisation of aniline in benzene solution, all at 20°.

Molar polarisation of solutions of aniline in benzene.

f_1.	ϵ.	$d_4^{20°}$.	P_1, c.c.	f_1.	ϵ.	$d_4^{20°}$.	P_1, c.c.	f_1.	ϵ.	$d_4^{20°}$.	P_1, c.c.
0·0519	2·480	0·8865	79·38	0·0626	2·512	0·8873	78·75	0·1604	2·872	0·9042	73·94

$P_{E+A} = 32·2$ c.c.; $P_\infty = 81·91$ c.c.; $\mu = 1·54 \times 10^{-18}$ E.S.U.

We wish to express our thanks to Dr. E. A. Moelwyn-Hughes, whose efforts made this work possible, and to Dr. G. H. Whiting, for help of various kinds. We are also indebted to the Chief Scientific Officer, Ministry of Supply, for permission to publish this note.—The University, Liverpool 3. [*Received, December 18th*, 1945.]

The Fries Reaction. Part II. On the Nature of the Substance described as 2-Hydroxy-1-benzoylnaphthalene (m. p. 175°).*

By Alexander Schönberg and Ahmed Mustafa.

Houben and Fischer (*Ber.*, 1927, **60**, 1777) directed attention to the fact that two different substances, m. p. 142° and m. p. 175°, are described as being 1-benzoyl-2-naphthol and, without carrying out experiments, they suggested that the latter substance is 3-benzoyl-2-naphthol. According to our observations, however, it is 6-benzoyl-2-naphthol, because on alkaline fusion we obtained 6-carboxy-2-naphthol, previously obtained by Butler and Royle (*J.*, 1923, **123**, 1654). In agreement with the new formula, the substance (m. p. 175°) couples with benzenediazonium chloride and is readily converted into a *methyl ether* by either diazomethane or methyl sulphate.

The formation of 6-benzoyl-2-naphthol is believed to be due to a Fries reaction: $C_{10}H_7{\cdot}OH(2) + CPhCl_3 \longrightarrow C_{10}H_7{\cdot}O{\cdot}CPhCl_2(2) \longrightarrow (6)CPhCl_2{\cdot}C_{10}H_6{\cdot}OH(2) \longrightarrow (6)\ Ph{\cdot}CO{\cdot}C_{10}H_6{\cdot}OH(2)$. Since, as a result of a Fries rearrangement, 2-naphthyl acetate gives 6-acetoxy-2-naphthol, but in only 5% yield (Witt and Braun, *Ber.*, 1914, **47**, 3231; cf. Fries and Schimmelschmidt, *Ber.*, 1925, **58**, 2837), whereas that of 6-benzoyl-2-naphthol is 70%, the latter is a suitable starting material for derivatives of 2-naphthol substituted in position 6.

6-Benzoyl-2-naphthol.—This substance was prepared according to Gesellschaft für Chemische Industrie in Basle, D.-R.P. 378,908 (cf. Friedlaender, "Fortschritte der Teerfarbenfabrikation," Bd. XIV, 1921—1925, p. 469), in almost colourless crystals, m. p. 175°. It is readily soluble in aqueous sodium hydroxide with an intense yellow colour and its alcoholic solution gives no colour with ferric chloride solution [Found: C, 82·1; H, 4·8; *M* (Rast), 231. Calc. for $C_{17}H_{12}O_2$: C, 82·2; H, 4·8%; *M*, 248]. Its solution in aqueous sodium hydroxide, when treated with a cold acid aqueous solution of benzenediazonium chloride, gives a bright red precipitate.

Fusion of 6-Benzoyl-2-naphthol with Potassium Hydroxide.—6-Benzoyl-2-naphthol (1 g.) was mixed with powdered potassium hydroxide (8 g.) in a nickel crucible and heated for 15 mins. at 240° (bath temp.); the temperature was raised to 280° and kept there for 5 mins. After cooling, the solid contents were dissolved in water (10 c.c.), and the solution was filtered, acidified with ice-cold dilute hydrochloric acid, and extracted with ether. The ethereal extract was washed with aqueous sodium carbonate and on evaporation gave 2-naphthol (identified by mixed m. p.). The aqueous sodium carbonate washings were acidified and extracted with ether; on evaporation colourless crystals were obtained which, on recrystallisation from water, proved to be 6-carboxy-2-naphthol, m. p. 245° (Butler and Royle, *loc. cit.*, give 241°). 6-Carboxy-2-naphthol is soluble in alcohol but difficultly soluble in benzene. Its alcoholic solution, when treated with ferric chloride in aqueous alcohol, gives an orange coloration as described by Butler and Royle (Found: C, 69·8; H, 4·4. Calc. for $C_{11}H_8O_3$: C, 70·2; H, 4·2%). The acetyl derivative, crystallised from water, had m. p. 220—221° (Butler and Royle give 221—223°).

2-Methoxy-6-benzoylnaphthalene was obtained by the action of methyl sulphate or of ethereal diazomethane solution on 6-benzoyl-2-naphthol. It crystallised readily from light petroleum (b. p. 80—90°), dissolved in hot ethyl alcohol, and was insoluble in aqueous sodium hydroxide. Its alcoholic solution did not give a colour with aqueous ferric chloride (Found: C, 82·4; H, 5·3; OMe, 11·5. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·3; OMe, 11·8%).—Fouad 1st University, Faculty of Science, Abbassia, Cairo, Egypt. [*Received, January 2nd*, 1946.]

* Schönberg and (Miss) Akila Mustafa, *J.*, 1943, 79, is regarded as Part I.

The Past and Future of X-Ray Crystallography.

THE HUGO MÜLLER LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY ON MAY 17TH, 1945.

By J. D. BERNAL, F.R.S.

THE relationship between chemistry and mineralogy, for the exposition of which these lectures were founded, cannot better be exemplified than in the subject of crystal chemistry. There, particularly since the discovery of the *X*-ray analysis of crystals, we find the explanation in physical and chemical terms for nearly all the phenomena of form and properties by which the older mineralogists classified their specimens. Through modern crystal chemistry, mineralogy has become a special branch of the general study of chemical combination in the solid state. But the origin of crystal chemistry goes back very much further than that of *X*-ray analysis. It is indeed practically contemporaneous with that of the recognition of crystals as objects for scientific study. In these early times we can distinguish three major periods: the period of Huyghens and Steno, the period of Lavoisier and Haüy, and the great nineteenth century period from Mitscherlich to Groth. The geometrical regularity of crystal form established by Steno in 1669 found an explanation by Newton and Huyghens in the later seventeenth century as representing the outward expression of regular arrangement of atoms. Newton, in his "Optics," talks of the atoms and the crystals being arranged in "rank and file." Huyghens goes much further in his attempt to explain the peculiar optical properties of the cleavage rhombs of Iceland spar. He notes with remarkable foresight how similar they are to the cleavage cubes of rock-salt but, as it were, squeezed along the cube diagonal, and explains this by postulating ellipsoidal atoms themselves optically anisotropic. If we take the CO_3 groups for these atoms this is almost the same model as used by Bragg in calculating the double refraction of calcite.

These early speculations, however accurate, required a much more extensive examination of crystals of different kinds before they could lead to a comprehensive understanding. This examination was carried out in the eighteenth century by collectors as a result of an increasing interest in mining. Through the influence of Linnæus the mineral kingdom began to acquire the same binomial classification as had been so successful with the animal and vegetable kingdoms. People still thought of minerals as growing in the earth in an almost organic way. Nevertheless it became apparent before the end of the century that the geometrical description based on angles was more certain than that based on general appearance and this led Haüy and Romé de Lisle to make the next logical step and discover the law of rational indices, itself a direct consequence of the "rank and file" definition of Newton. From now on crystal species could be defined precisely by a minimum number of parameters, the axial ratios, and descriptive crystallography became an exact science.

The connections of this science with chemistry were very close from the outset. The new nomenclature of Lavoisier and its extension through Dalton's atomic hypothesis helped to establish the idea that every definite chemical compound had an equally definite crystallographic form. But this law was soon found to be doubly defective. The same chemical substance was often found to have different crystal forms (polymorphism, discovered by Mitscherlich in 1821), and different chemical substances to have the same crystal form (isomorphism, discovered by Mitscherlich in 1819). Isomorphism provided the first positive and useful connection between crystallography and chemistry. It served to indicate likenesses between elements and thus, in the hands of Berzelius and Mendeléeff, to determine the valencies of beryllium, tellurium, and indium, besides predicting those of germanium and scandium.

All through the nineteenth century crystallography went hand in hand with chemistry; the chemists analysed new minerals described by the crystallographers, the crystallographers measured crystals of new substances prepared by the chemists. This produced a vast mass of material, represented on the one hand by the classical text book of Dana's "Mineralogy" and on the other by Groth's "Crystal Chemistry." This crystallographic work was of immediate and permanent value both for identification of mineral and chemical substances and for classification. In the middle of the century crystallography contributed to chemistry in an entirely different way when Pasteur resolved tartaric acid by picking out right- and left-handed crystal forms and thus laid the foundations of stereochemistry.

While all this was going on the theorists were not idle. Successively, the fourteen space lattices were established in 1850 by Bravais, the thirty-two crystal classes in 1866 by Gadolin and Von Lang, the sixty-five rotational space groups in 1879 by Sohncke, and, finally, by a magnificent triple effort, the 230 space groups by Schoenflies, Feodorov, and Barlow in 1890. All these workers held as their basic assumption that crystals were built up from regular arrangements of atoms; they had determined with more and more completeness what the geometrical possibilities of such arrangements might be. But they still lacked any clue as to what the actual arrangements of any atoms were in any crystal. Crystallography, however exact and mathematical, remained a descriptive science.

There have been few examples in the history of science more dramatic than the discovery of the diffraction of *X*-rays by crystals by Laue in 1912 and its almost immediate application to the analysis of crystal structure by the Braggs in 1913. What had been previously a totally unknown world was almost at the outset reduced to order and measure. Yet there was a link between the older crystallography and the new structure analysis. Barlow may be reckoned as a prophet of structural crystal chemistry; he anticipated the explanation of close packing of metals and actually put forward the correct structure of rock salt as early as 1906. Unfortunately his association with Pope in the delusive valency-volume theory has led to his contribution being almost completely overlooked.

The effect of Sir Lawrence Bragg's determination of the rock-salt structure was completely revolutionary in more than one direction. The fact that it showed the crystal to be composed of ions with no trace of molecules upset the older chemists for whom the chemical molecule was a legitimate end of all structural research—including such mighty molecules as are even to this day postulated for the micas and felspars. But it did more. It introduced the true metrical atom scale to chemistry. It showed that the atomic theory with its structural formulæ that Ostwald had considered near the end of the nineteenth century merely as a convenient hypothesis was in fact a precise spatial description. The " billiard ball " atom was back again and this time with its size directly measured. The early structures worked out by the Braggs covered, as we now know, practically the whole range of the major structure types of crystal chemistry. Rock-salt, blende, pyrites, diamond, naphthalene, were the archetypes of all the more complicated structures that we study to-day. To complete the picture, all that was needed was the determination of close packed metal structures by Debye and Hull.

At first the world revealed by these crystal structures—a world as startling as and far more important to us than that shown by Galileo's telescope—was difficult to understand on the basis of older chemical preconceptions; particularly difficult was the relation between the metals and their salts. Following Lothar Meyer's table of atomic volumes, it seemed rational at first to take the metal atoms as large and the non-metal atoms as small, and it was not until the time of Goldschmidt in 1928 that the modern clear distinction between the small metal ion and the large metal atom were realised. Goldschmidt, with his extensive work on simple compounds, laid the basis for metrical crystal chemistry and closed the first—what may be called the heroic—period of crystal chemistry.

It was by then apparent that the solid state could not be explained by one set of laws: that there were, as Fajans and Joos had pointed out, four major types of solid—metallic, ionic, adamantine, and molecular—with any number of intermediate types and sub-types. These types of structure depended on the predominance, in the final building up of the structure, of the metallic, ionic, co-valent, and van der Waals forces, the explanations of which were appearing in contemporary theoretical chemistry with the advent of the new quantum theory. From then on it is reasonable to state that the history of crystal chemistry developed along three main lines—metallic, ionic, and molecular. (The adamantine class represented by diamond itself and a few other very hard substances has not been extensively studied and its physics are still in the stage of acute but probably fruitful controversy.)

It was clear long before the advent of crystal chemistry that the laws of combination of elements in alloy structures had little in common with those prevailing in the rest of chemistry. Intermetallic compounds, it is true, did exist but these were very far from being chemically identifiable substances of invariable composition, and when their composition was determined it often corresponded to no simple stoicheiometric ratio. It was clear that the rules of ordinary chemistry simply did not apply to metals. Crystal chemistry almost from the first shed light on this situation. It showed that the great majority of metals and alloys were characterised by the one common property of close atomic packing, embracing relatively trivial distinctions involving small energy changes between the three canonical types of cubic face centred, hexagonal, and cubic body centred packing. Where more complicated structures occurred they could be derived from the simple ones by slight distortion or internal arrangement as in the classic case of α-brass. In simple solid solution alloys, atoms of different kinds seemed to be arranged entirely at random, though careful cooling in certain cases brought about disorder–order transformation theoretically explained by Bragg and Williams.

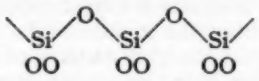
The great work of Westgren, who pioneered the *X*-ray studies of particular alloy systems, showed that phases of corresponding structures did not have corresponding chemical formulæ. This was explained through the brilliant intuition of Hume-Rothery's rule which stated the fundamental law of metal crystal chemistry —that the structure of a metallic compound is a function of the ratio of the number of free electrons to the number of atoms and is, apart from geometrical effects, due to markedly different sizes of positive ions, independent of the chemical nature of the elements which form the compound. The emphasis thus placed on the electron fitted in with the newer conception of a degenerate electron gas as the cohesive medium in metals and led to the explanation of the Hume-Rothery rules by Jones in terms of the Brillouin zones of electron energy discontinuities whose form determines the stability of the metal crystal lattice. Since that time the intricacies of metal crystal chemistry have been more and more studied, particularly by the school of Bradley and Lipson. Most of this work tended to bring out for the first time the relations between the constituents of metals and alloys and those mechanical and electrical properties of strength, ductility, conductivity, permeability, and coercivity which are all-important in the industrial uses of metals and alloys and which could not conceivably be derived from a mere knowledge of their chemical composition. The elucidation of order–disorder phenomena, together with that of the mechanism of separation of phases of very similar energies, led to an explanation of the phenomena of age-hardening and hysteresis which can now be analysed and predicted with increasing accuracy. There is clearly here an enormous field for future work, one in which comprehensive theory of the fundamental processes involved will come to take the place more and more of the extremely empirical methods that have hitherto ruled in metallurgy.

The effect of *X*-ray studies on inorganic chemistry have been almost as revolutionary as those on metallurgy. This is the field that mineralogy and chemistry have in common and it can be said that structural analysis has reduced what was previously a confused domain to an exact science. The initial discovery that sodium chloride contained ions and not atoms was the starting point for a logical building up of the laws of combination of charged particles held together by Coulomb forces. The extremely simple structures of the alkali halides and alkali earth oxides made it possible for Born and his co-workers to provide an almost complete theory of the

interaction of ions and to predict interatomic distances and forces from a knowledge of the quantum physics of the atoms of which they were composed. In no other part of chemistry has anything like this degree of accuracy been achieved. Born showed, however, that the crystallographic differences that exist between the different forms correspond to very small changes of energy and that consequently the prediction of precise structures will always be fraught with great difficulty.

The general principles, however, of ionic crystal chemistry were clear. The dominating conception that the packing of ions of one sign round ions of the other and the major factors that influenced this packing appeared to be the simple electrical geometric factors of ion charge and ion radius. These principles were applied by Pauling in his celebrated rules for the structure of ionic crystals which are based on the conception of ionic valency, defined as the ratio of the charge on an ion divided by the number of ions of the opposite sign in its co-ordination polyhedron. They are equivalent to the hypothesis that the lines of forces originating on any ion of a stable structure terminate on ions of the opposite sign in its immediate co-ordination polyhedron.

While these rules were being elaborated, the great work of the Manchester school under Sir Lawrence Bragg had established the structures of the most complex, though the most common, of inorganic substances—the silicates. The general classification of the silicates arrived at by the mineralogists by chemical and morphological means was found to correspond extraordinarily well with the logic of their structures. The basic silicates contained separate SiO_4^{4-} groups, the metasilicates having instead of the ion SiO_3^{2-} the polypyrosilicate ion



which gave them their fibrous qualities. The fissile micas and clays in turn depended on an aluminosilicate sheet ion, $(SiAl)_2O_5$, and, finally, the acid silicates such as the felspars had complete aluminosilicate framework ions, $(AlSi)O_2$, in which were inserted positive ions to balance the charge. Thus, in the place of the complicated and unreal formulæ for the molecules of silicates, the Bragg school developed structural interpretations into which the complex replacement rules of the nineteenth century mineralogists fitted most naturally, showing here again the dominance of ionic size in ionic chemistry.

The same success followed the later work on the structure of complex ions and co-ordinated compounds. It now appeared that the whole of inorganic chemistry, as far as the structure of low energy phases was concerned, could almost be deduced from a knowledge of a few properties of the ions. How far this work has progressed is well illustrated in A. F. Wells's new text book on " Structural Inorganic Chemistry." The ionic approach to chemistry, however, is very simple except when either small, highly charged, or large easily deformed ions are involved; here it passes over, by something like the correspondence principle of Bohr, into homopolar chemistry. There is a large field where a particular atomic combination is undoubtedly held together mainly by electron exchange forces but at the same time carries localised charges which are all-important in their relation to other elements of the crystal. A particularly important example of this, because of its all-pervasiveness in chemistry, is that of hydrogen. Hydrogen, attached to nitrogen or oxygen, forms a highly localised dipole the strength of which depends very much on the other attachments of the nitrogen or oxygen atom. The more polarising this is, as for example in the series of Na^+, Mg^{2+}, Al^{3+}, Si^{4+}, P^{5+}, S^{6+} hydroxides, the easier it is to detach the hydrogen ion. The alkaline–acid series finds its expression in the strength of the hydroxyl and hydrogen bonds.

Another range of deviation from simple ionic considerations is found to be due to the polarisability of atoms, particularly those of the lower rows of the periodic table. With sulphur and chlorine, and even more with tellurium and iodine, the distortion of the anion by polarisation comes to play a leading rôle. Where the cations are also polarisable or have electron defects in their inner shells, the structures of the crystals containing them deviate more and more from the ionic expectations and approach more closely those of metals. This is a sphere which as yet has not received anything like the attention it deserves from *X*-ray crystallographers. The whole range of minerals of the sulphide–arsenide–antimonide groups are still, except for their simplest members, unstudied. Considering their importance in mining and smelting practice this study would seem well worth undertaking

In organic chemistry the crystal chemical position is very different from that in the other fields. Here the molecule is a real physical entity and its structure can be—and is—elucidated by means of extraordinarily subtle and complex logic based on chemical transformations. It was perhaps not surprising, therefore, that for many years crystal analysis could do little more than confirm the structures already well known to the organic chemist. However, in the later twenties, the work of Sir William Bragg's school, particularly Lonsdale, Robertson, and Cox, showed that even with well-known organic compounds there was much to be learned from crystal analysis. The chemical formula, hitherto purely topological, could in the hands of the crystal analyst become geometrical. Bond lengths and angles came to be measured with greater and greater accuracy, and these measurements themselves tended to show what was already becoming apparent for quantum chemical reasons, that the old distinctions between single, double, and treble bonds could not be maintained, but that every bond was to a certain extent *sui generis* and its finer points could only be explained in relation to the molecule as a whole.

X-Ray analysis, however, did not rest there. Robertson and Woodward in 1940 succeeded in achieving for the first time in organic chemistry what the Braggs had previously done in inorganic chemistry, the determination of a complete structure without any chemical assumptions. Their classic analysis of phthalocyanine

demonstrated physically for the first time that organic structural formulæ corresponded to physical realities. In other words had there been no development of organic chemistry, *X*-ray analysis, based on nothing more than the mathematical theory of diffraction, could have determined the structure of organic molecules.

Meanwhile another application of *X*-ray analysis was being made in a far cruder way. From cell sizes and general indications as to molecular orientation it had been possible, without being able to deduce precise formulæ, to discriminate with certainty between rival formulæ for naturally occurring substances. In this way the modern, accepted carbon skeleton of the sterols was determined and its relationship with that of the sex hormones and cardiac poisons established. *X*-Ray analysis was to prove a most powerful weapon in speeding up the work of the chemist in determining the structure of unknown substances.

These two approaches were combined in the work of Mrs. Hodgkin who, after completing with Carlisle a detailed absolute analysis of cholesteryl iodide, applied the full battery of *X*-ray analytical technique to the structure of penicillin, a molecule of most unusual type, and succeeded in determining its structural formula well in advance of its chemical analysis. Full proof of this formula can only come when penicillin has been synthesised, but in the meantime it has been demonstrated that any compound capable of being crystallised in association with a heavy atom or ion can be completely analysed by *X*-ray methods. Sooner or later this will lead to a major revolution in chemical analytical technique.

While *X*-ray methods were showing their value in the field of classical organic chemistry, they were also being used at the other end of the scale to elucidate the most complex examples of biological structures: those of natural polymers such as polysaccharides, the nucleic acids, and, above all, the proteins. The pioneer work of Astbury on organic fibres established the basic pattern of polypeptide chains underlying the structure of hair, muscle, and tendon and showed that in the whole range of animal life there appeared to be only two major arrangements—the keratin–myosin type which could exist in a stretched or curled form, thus giving the first hint as to the molecular nature of biological contractility and the action of muscle, and the more inert collagen chains of connective tissue.

In contrast to these fibrous proteins, the soluble crystalline proteins were found to consist of large but perfectly definite globular molecules whose structures are being attacked at the present day by the schools of Mrs. Hodgkin and Drs. Perutz and Fankuchen. It is in the analysis of protein structure that the *X*-ray method is being pushed to its utmost. In conjunction with all other physical methods, with chemical analysis, centrifugation, and electrical measurements, we may yet hope in the near future, if not to determine the complete structure of these vastly complicated molecules, at least to understand the principles on which they are constructed and to make use of that knowledge in the fields of biology and medicine.

This necessarily brief survey of the field of structural crystallography almost inevitably, of itself, points towards the future. Many of the lines of advance are inherent in the work already being done and are in fact actively being pursued; but it may be worth while examining the field as a whole in order to see whether this progress is as widespread or as intense as it should be in relation to its possible importance both as an intrinsic study and for other sciences. By now the actual methods of *X*-ray crystallography have been brought to a remarkable pitch of perfection. The old trial and error methods of the " heroic " period have been superseded by a logical and precise sequence of manageable mathematical operations. The gain in accuracy and scope has been attained, however, only at the expense of a far greater laboriousness involving an enormous increase in man-hours per structure. Even with mechanical aids the labour involved in crystal analysis is bearing heavily on the meagre resources of *X*-ray crystallographers. For a structure like penicillin several hundred intensities had to be accurately measured and in all several thousand computations made. When it is realised that for hæmoglobin 8,700 intensities have already been measured, the magnitude of the task can be seen. Nevertheless this development is in line with the general tendency of modern science where results far more valuable than any that our ancestors dreamed of can now be obtained with certainty but only by carrying out the operations of scientific discovery itself on a semi-industrial scale. This implies, further, that the choice of substances to be analysed has to be planned and cannot be left to chance or caprice. For this the closest collaboration is absolutely necessary between chemists, engineers, and biologists; but the full battery of analytical method does not need to be turned on to every chemical problem; there are thousands where some comparatively simple measurement of cell size or space group is adequate to save the chemist many weeks of laborious work.

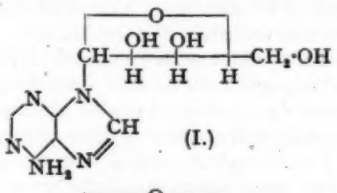
It is clear from this that the organisation of *X*-ray crystallography should be two-fold. We must have highly specialised analytical centres working as part of big chemical enterprises and, at the same time, a wide distribution of *X*-ray apparatus and the knowledge of how to use it in every chemical laboratory, routine as well as research. Naturally in certain fields, notably metallurgy, the value of routine *X*-ray examinations has been recognised by equipment manufacturers, and the substitution of the Geiger counters and electrostatic recording for the photographic plate makes it possible to devise automatic checks for the structural quality of any product. All this implies the introduction of the knowledge of structure analysis much earlier and much more widely in chemical curricula. It is a disgrace, for which the war is, however, in part responsible, that we have only one school in the whole of England where structure analysis is systematically taught; it is consequently looked on somewhat as a mystery and it is difficult for any chemist brought up on existing lines even to understand the meaning of its results. This will certainly come about in time but it is to be hoped that with the new turn towards making chemistry an exact science and less of a formulary, and with the increased recognition of the interdependence of the sciences, the change will be welcomed and even assisted by the main body of chemists.

Synthesis in the Study of Nucleotides.

THE PEDLER LECTURE, DELIVERED IN BIRMINGHAM ON FEBRUARY 12TH, 1946, AND IN LONDON ON MARCH 7TH, 1946.

By A. R. TODD, M.A., D.Sc., F.R.S.

THE term nucleotide covers a very large number of natural substances ranging from such comparatively simple compounds as muscle adenylic acid, through co-enzymes such as adenosine triphosphate important in phosphate transfer or riboflavin-adenine-dinucleotide, the prosthetic group of many flavoproteins, to the nucleic acids (polynucleotides) which, associated with proteins, form the nucleoproteins embracing substances intimately concerned with the reproduction of living cells as well as the causative agents of certain diseases (plant viruses). All these are structurally related and can be regarded as built up of basic units each consisting of a cyclic nitrogenous substance (usually a purine or pyrimidine) combined with a sugar (usually *d*-ribose or 2-deoxyribose) and phosphoric acid. The simplest nucleotides are single units and the others vary in complexity up to the polynucleotides in which the molecule may contain a very large number of units linked together. The importance of the nucleotides in the chemistry of living matter can hardly be over-estimated and it is therefore not surprising that they are increasingly attracting the attention of organic chemists. From the chemist's standpoint the macromolecular nucleic acids present structural problems resembling those encountered in the study of proteins. Whilst proteins, however, frequently contain twenty or more different amino-acid residues, present knowledge suggests that nucleic acids are normally of two types—ribonucleic and deoxyribonucleic—each built up from some four different simple nucleotide units. This makes the problem of their structure at once easier and, in certain directions, more difficult to solve. The structure of the nucleic acids has been the subject of investigations by many workers during the past thirty or forty years. Much has been learnt as a result regarding the fundamental units of some of the more accessible, although of the nature of the polynucleotides themselves our knowledge remains scanty. It is not my purpose to discuss here the degradative work on polynucleotides. I shall, however, touch on the results of such work on the simpler nucleotides where they are relevant to or arise from my main theme, which is an account of an approach to the nucleotide problem using synthetic methods. This approach must obviously begin with the simplest units and work up to the complex, and it has been and remains a major interest in my laboratory. In this lecture I propose to outline to you the pattern and development of our researches as far as they have gone. In so doing I act as spokesman for a group of enthusiastic colleagues with whom it has been my good fortune to be associated and to whom should be accorded the credit for the progress which has been made.



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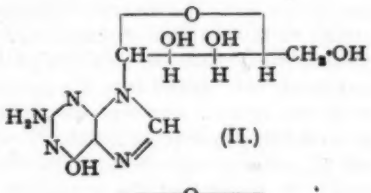

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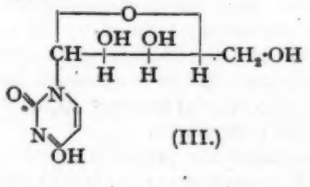

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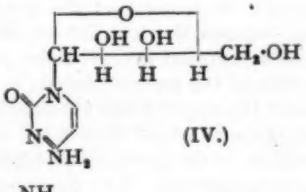

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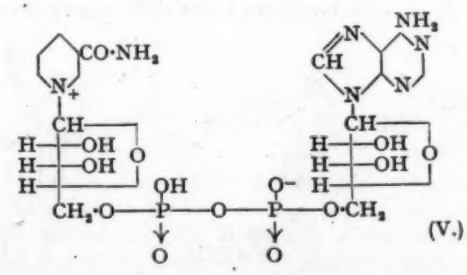

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At this point it may be well to consider the structures, as far as known at the commencement of our researches, of some simple nucleotides obtained by suitable hydrolytic breakdown of polynucleotides.[1] From ribonucleic acids one obtains the 3′-phosphates of the glycosides (ribonucleosides), adenosine (I), guanosine (II), uridine (III) and cytidine (IV). The structures of these compounds have been cleared up in most essentials by analytical methods. In each case the structure of the aglycone is certain, the sugar residue is known to be *d*-ribofuranose, and the position of the phosphate group on C_3 of the sugar chain has been established. In the

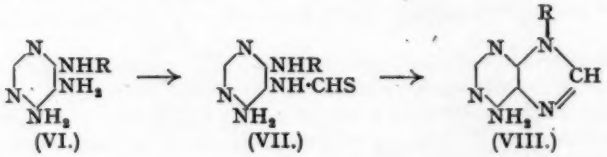
case of the purine derivatives the glycosidic linkage was early shown to be at N_7 or N_9 in the iminazole nucleus, but the only evidence hitherto advanced to distinguish between these possibilities is that of Gulland and his collaborators [2] who concluded on spectroscopic grounds that the sugar residue was attached to N_9—a conclusion which has been generally accepted. In my own view the N_9 location is also rendered highly probable by the fact that this position in the purines corresponds to N_9—the point of attachment of the ribityl residue—in riboflavin, a substance which is probably biogenetically related to the purine nucleosides. In the pyrimidine nucleotides the location of the sugar residue at N_3 was adequately established.[3] Whether the natural compounds are α- or β-glycosides remained unknown.

Of the four deoxyribonucleotides obtained by hydrolytic breakdown of deoxyribonucleic acids less is known, and their formulation rests largely on analogy with the ribonucleotides. They are hydrolysed to 2-deoxyribose, phosphoric acid, and adenine, guanine, cytosine, and thymine respectively. The furanose nature of the glycosidic residue, demonstrated only in the case of thymidine,[4] is generally assumed, as is the location of the phosphate grouping at C_3 in the sugar chain. In the purine deoxyribosides spectroscopic evidence again suggests attachment of the sugar to N_9.[2]

Although any synthetic approach to the nucleotide problem must ultimately lead, if successful, to the nucleic acids, my colleagues and I entered this field with more limited initial objectives. We had been interested in the question of the specificity of B vitamins, several of which are components of nucleotide molecules which exercise co-enzyme function, *e.g.*, cozymase (V), riboflavin-adenine-dinucleotide. We wished to find out more about the factors governing the specificity of such co-enzymes and their linkage with apoenzymes. To do this we decided to investigate the possibility of total synthesis of such substances by methods which would be general and sufficiently flexible to permit the synthesis of variants of the molecule at will. In this way we hoped to obtain a range of compounds which might be of value in furthering the study of co-enzyme function, and possibly in opening the way to the production of highly specific chemotherapeutic agents acting by a competitive mechanism. Taking the molecule of cozymase (V) as an example it is clear that the problem of synthesis at once resolves itself into three parts: (*a*) the synthesis of nucleosides, (*b*) the phosphorylation of sensitive molecules (*i.e.*, nucleotide synthesis), and (*c*) linkage of molecules through phosphate or polyphosphate residues (*i.e.*, polynucleotide synthesis). All three have occupied our attention, but it will be convenient to deal with each in turn commencing with the synthesis of nucleosides. Although there has naturally been some overlap through various lines being pursued simultaneously, the order in which they have been named does correspond roughly to the pattern of our investigations. The nucleoside problem is epitomised in the substance adenosine (I), probably the most important of all the nucleosides, and I propose first to discuss, in the main, experiments directed to the total synthesis of this and related purine glycosides.

Although no natural purine or pyrimidine nucleoside has been synthesised numerous attempts have been made in the past to do so. The nearest approach has been that of Hilbert and Rist who synthesised 3-*d*-ribopyranosidouracil.[5] In the case of the purine nucleosides previous synthetic attempts have been of two types. In the first of these the silver salt of a purine has been caused to react with an acetohalogeno-sugar and the desired substituents introduced into the purine nucleus by subsequent operations. This method was used in the pioneer work of Fischer [6] who was able in this way to synthesise a number of purine glucosides including those of adenine and theophylline in which, on spectroscopic grounds, the glucose residue is considered to be located at N_9 and N_7 respectively. Whilst this method does offer a route to the naturally occurring compounds it would require for its realisation the use of the hitherto unknown acetohalogeno-ribofuranose and it is not unambiguous as regards the location of the sugar residue in the products obtained by its use. The second type of synthesis attempted involved the preparation of a glycoside of a pyrimidine or an iminazole with subsequent completion of the purine nucleus by building on the second ring. All such attempts had failed through inability to obtain the appropriate intermediates, but nevertheless this type of method appeared to be the most suitable for our purpose which demanded unambiguous and flexible procedures.

In our approach to the problem of adenosine synthesis we envisaged the preparation of a 5 : 6-diamino-4-glycosidaminopyrimidine (*e.g.*, VI; R = *d*-ribofuranose) followed by conversion of this into the required purine

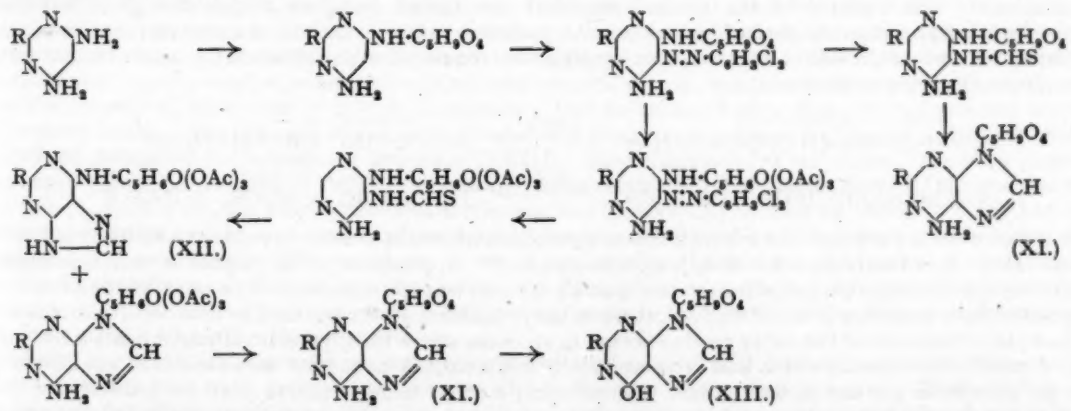


derivative. This method is, of course, based on the Traube synthesis of adenine in which a compound of type (VI; R = H) is heated with formic acid, the initially produced formamido-compound cyclising at higher temperatures by loss of water. The first essential was to devise a milder cyclisation procedure which would

avoid the danger of hydrolysis inherent in the Traube procedure if applied to sensitive glycosides. Such a procedure was found when it was shown that a 5-thioformamido-compound (VII; R = H), prepared from (VI; R = H) by treatment with aqueous sodium or potassium dithioformate, passed into the corresponding purine on heating in dry pyridine, hydrogen sulphide being evolved.[7]

For the synthesis of a 9-substituted adenine derivative by this route an intermediate (VII) would be necessary, and the question at once arises whether cyclisation will proceed in the desired direction to give (VIII) and not (IX). Initially the problem was tackled in model experiments in which R = alkyl, and various readily accessible pyrimidine derivatives analogous to (VII) were employed bearing substituents in the 2-position (*e.g.*, MeS). It seemed to us probable that ring-closure would in fact lead to the desired 9-alkylpurine, since general experience of the behaviour of pyrimidine derivatives suggested that a compound such as (VII; R = alkyl) would tend to react as if it had structure (VIIa) in which case cyclisation by loss of hydrogen sulphide would be expected to give (VIII) and not (IX). This expectation was realised on experiment; cyclisation of (VII) gave (VIII) exclusively and in almost theoretical yield.[7] Assuming that a 4-glycosidamino-group would be analogous to a 4-alkylamino-group the way then seemed clear for the synthesis of a 9-glycosidoadenine.

The next problem to be solved was the synthesis of a 5 : 6-diamino-4-glycosidaminopyrimidine of type (VI) and it was clear that the only practicable method would be preparation of a 6-amino-4-glycosidaminopyrimidine and subsequent introduction of the 5-amino-group. Hitherto 4-glycosidaminopyrimidines had defied all attempts at preparation. For this the principal reason undoubtedly lay in the normal tendency of 4-aminopyrimidines to react in the tautomeric imino-dihydropyrimidine form; in this form glycosidisation could hardly be expected. If, however, we consider the tautomeric possibilities in substituted pyrimidines, it is evident that in 4 : 6-diaminopyrimidines of type (X) where R is H, alkyl, or some substituent other than a group (*e.g.*, OH, SH, NH_2) capable of taking part in prototropic change, one double bond must occupy position 1 : 2 or 2 : 3 and hence one of the amino-groups at positions 4 and 6 should show in considerable degree the behaviour of a true amino-group and as such be capable of glycosidisation. In accordance with this view we were able to condense 4 : 6-diaminopyrimidines fulfilling these conditions with pentoses and hexoses by heating in absolute alcohol in presence of an acidic catalyst under conditions which allowed continuous removal of the water liberated in the reaction.[8] Having obtained by this means the desired 6-amino-4-glycosidaminopyrimidine derivatives it was our original intention to introduce a 5-amino-group by nitrosation in acetic acid solution followed by reduction, but this was possible only in the case of glycosides bearing a methylthio-group in position 2 to facilitate nitrosation. In all other cases nitrosation in position 5 required the use of mineral acids, and the method could not be employed because of consequent hydrolysis of the glycoside. Fortunately a suitable alternative became available when it was found that reactive diazonium compounds such as those from *p*-chloroaniline or 2 : 5-dichloroaniline couple in weakly alkaline solution with 6-amino-4-glycosidaminopyrimidines to give crystalline azo-compounds which can be reduced catalytically to the desired 5-aminoderivatives.[9] The latter can then be thioformylated and cyclised to purine derivatives. The synthetic route thus established was applied successfully to the first unambiguous syntheses of 9-pentosidoadenine derivatives as indicated schematically below :[10]

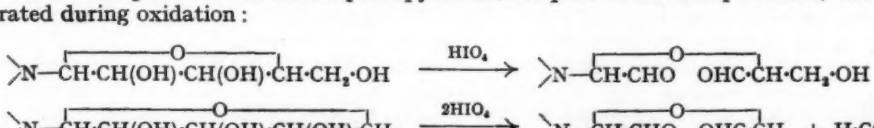


The use of acetylated thioformamido-compounds in the final cyclisation was found to give better yields, but in a number of cases (*e.g.*, in the xylose series when R = H, Me, or MeS) a mixture of the 6-glycosidaminopurine (XII) and the 9-glycosidoadenine (XI) was obtained. These two products are readily distinguished by the solubility of the former in alkali and the insolubility of the latter coupled with its ready deamination to the corresponding 9-glycosidohypoxanthine (XIII). This production of isomeric glycosides never, so far as we know, occurs when acetyl-free thioformamido-compounds are used or when the cyclisation medium—alcoholic sodium alkoxides in our more recent work—is such as to cause preliminary deacetylation. As it is in direct contrast to our experience in the model experiments on the synthesis of 9-alkylpurines, some explanation is required. We believe that the explanation lies in chelation between the glycosidic NH-group and the acetyl group at C_2 in the sugar chain. Such chelation, which is sterically feasible, would clearly increase the basicity

of the glycosidic nitrogen and hence, indirectly, of the nitrogen at position 6 thus enabling it to take part in the cyclisation process.[11, 12] This explanation is supported by all available evidence and is much more satisfactory than any based on steric hindrance. The magnitude of the chelation effect seems to vary considerably from case to case and cannot at present be predicted on theoretical considerations.

The synthetic method illustrated in the above scheme has been applied to a variety of adenine and substituted adenine hexosides and pentosides, but that application has been complicated in two cases—those of the *d*-xylosides of adenine [11] and 2-methylthioadenine [13]—by the occurrence of two series of isomeric intermediates in the earlier stages of the syntheses. These phenomena were for a time a source of confusion but they have been eventually clarified and a satisfactory explanation is now available. The simplest way to deal with this topic is to consider a specific case—that of the synthesis of 9-*d*-xylosido-2-methylthioadenine (XI; R = MeS). Xylosidisation of 4 : 6-diamino-2-methylthiopyrimidine gives a mixture of two isomeric *d*-xylosides which yield distinct 5-nitroso- and 5-arylazo-derivatives. Reduction of these to a 5-amino-compound, however, causes the isomerism to disappear so that only one 5-thioformamido-compound and one 9-*d*-xylosido-2-methylthioadenine can be obtained. Similarly, acetylation of the 5-nitroso-compounds causes disappearance of isomerism. It is clear that this isomerism must have its origin in the sugar residue, *i.e.*, it could be furanose-pyranose or α-β in type. In fact careful study of all the data leads to the conclusion that the two series of intermediates are α-β-isomers—which is perhaps not surprising in view of the analogy between their mode of preparation and Fischer's classical condensation of glucose and methanol to give α- and β-methylglucosides. The reason for the merging of the two isomeric series by interconversion during the course of the purine synthesis has been the subject of much study; it appears to fit into the general behaviour of *N*-glycosides and to be essentially similar to the phenomenon of mutarotation.[14] This is hardly the place to develop lengthy theoretical arguments but, in brief, it is believed that in those cases where separate α- and β-isomers are obtained they are compounds so weakly basic that the velocity of mutarotation is vanishingly small. As soon as the basicity of the glycosidic nitrogen atom is increased, either indirectly by introduction of a 5-amino-group or directly by chelation in the case of acetylated compounds (see above), interconversion (mutarotation) can and does occur and, one isomer being much more stable, it is complete. It has been concluded from optical data that in all the pyrimidine derivatives so far prepared it is the β-glycoside which is the stable form.[14]

A substance of particular interest among those synthesised by the above method is 9-*d*-ribosidoadenine.[15] This synthetic glycoside, although indistinguishable from adenosine in its ultra-violet absorption, is nevertheless not identical with it. Clearly there are three possible reasons any or all of which might account for the difference. First, the synthetic substance might be a pyranoside, the natural nucleoside being a furanoside; secondly, the difference might be due to α : β-isomerism; and finally, although much less probably, the earlier spectroscopic evidence might have been misinterpreted and the sugar residue in the natural compound might be located at some point other than N_9. The obvious first step was to seek some general method for determining lactol ring-structure in purine glycosides which could be rapidly and conveniently carried out on small amounts of material. Such a method became available when it was shown that the periodate oxidation procedure developed by Hudson and his collaborators for the *O*-glycosides could be applied successfully to tertiary *N*-glycosides.[16] The validity of the method was first established using as models theophylline-7-glycopyranosides and natural purine-9-ribofuranosides. As indicated below, oxidation of a pentofuranoside requires an uptake of 1 mol. of periodate whereas a pentopyranoside requires 2 mols. of periodate, and 1 mol. of formic acid is liberated during oxidation:



On titration with periodate the synthetic adenine riboside absorbed 2 mols. of oxidant and liberated 1 mol. of formic acid; it is therefore a 9-*d*-ribopyranosidoadenine.[15] Application of the periodate oxidation method to our other synthetic purine xylosides showed that all of them were pyranosides. The same method could not be applied to determination of lactol ring-structure in the pyrimidine glycosides used as synthetic intermediates, since complete oxidation of the sugar residue occurs in all cases where the glycosidic nitrogen bears a hydrogen atom. A modified method in which lead tetra-acetate was substituted for sodium metaperiodate was also found to be too unreliable for use in such cases. Nevertheless a pyranoside structure may be deduced for these intermediates since otherwise one would have to assume furanose-pyranose interconversion in fully acetylated derivatives during the course of purine synthesis.

The periodate oxidation method has proved a most valuable tool in our investigations and it has been applied to a variety of problems. Some of these concern the nucleotides proper and will be discussed later; for the moment attention will be confined to the determination of configuration at the glycosidic carbon atom in natural and synthetic nucleosides and to the rigid proof of the attachment of sugar at N_9 in the natural purine nucleosides. Knowledge of the glycosidic configuration of the natural nucleosides is of considerable importance from a general viewpoint although it does not appear to have been the subject of any previous investigations. Configuration at the glycosidic centre in the nucleosides must be a major factor in determining the molecular packing in polynucleotides and in governing their linkage with proteins in nucleoproteins. In attacking this problem experimentally we have made the usual assumption that glycosides prepared by the use of *cis*-α-

acetohalogeno-sugars have the β-configuration. Fischer and Helferich,[6] by the interaction of silver dichloroadenine and α-acetobromoglucose followed by removal of halogen atoms from the product and deacetylation, obtained a glucoside which may be described as adenine 9-β-*d*-glucopyranoside, the location of the sugar resting on spectroscopic evidence. Periodate titration of this substance proceeded with uptake of 2 mols. of oxidant yielding a dialdehyde. Since the configuration at C_4 in *d*-ribose is the same as that at C_5 in *d*-glucose, and since all other asymmetric centres save C_1 are destroyed on periodate oxidation, then if adenosine is a β-glycoside it should on periodate oxidation yield the same dialdehyde. This was found to be the case and it is concluded that adenosine is a β-*d*-ribofuranoside.[17] Since it was also established that synthesis of 9-*d*-glucopyranosidoadenine [18] by our general method gives a product identical with the glucoside of Fischer and Helferich, it follows rigidly that the sugar residue in adenosine is at N_9 and that this nucleoside is correctly described as 9-β-*d*-ribofuranosidoadenine. By an extension of this method a β-configuration has been established for all the purine glycosides synthesised by our general procedure outlined above.

In analogous fashion it has been shown [17] that the natural pyrimidine nucleosides uridine and cytidine can be oxidised to dialdehydes identical with those obtained from 3-β-*d*-glucopyranosidouracil and 3-β-*d*-glucopyranosidocytosine, and it follows that these nucleosides are respectively 3-β-*d*-ribofuranosidouracil and 3-β-*d*-ribofuranosidocytosine.

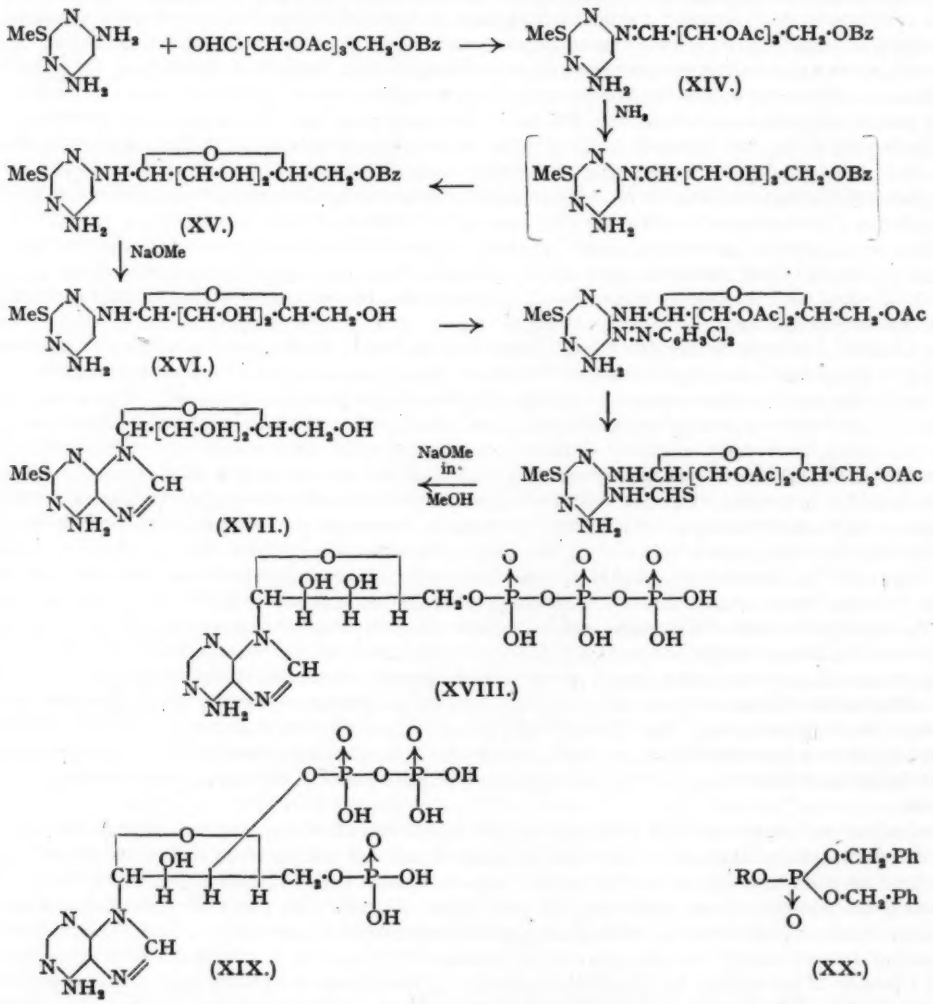
On the basis of the work so far described it may be concluded that a total synthesis of adenosine could be achieved by the synthetic route worked out for the 9-glycopyranosidoadenines provided that a 6-amino-4-*d*-ribofuranosidoaminopyrimidine, necessary as starting material, could be prepared. The preparation of such a compound, however, presented considerable difficulty; the obvious methods—condensation of 4 : 6-diaminopyrimidines with fully acylated furanose sugars or with 5-acylpentofuranoses—failed to yield the desired product. The problem was finally solved by application of a novel glycosidisation procedure.[19] It was first established that the methylthio-group in 4 : 6-diamino-2-methylthiopyrimidine increases the basic character of the amino-groups sufficiently to enable one of them to condense with benzaldehyde to form a Schiff base. In the same way it could be condensed with the aldehydo-sugar 5-benzoyl 2 : 3 : 4-triacetyl *l*-arabinose giving the Schiff base (XIV). Treatment of this product with cold methanolic ammonia removed the acetyl groups leaving the benzoyl group unaffected. The initial product, presumably a Schiff base, isomerised at once to the 5-benzoyl *l*-arabinofuranoside (XV) from which the benzoyl group could subsequently be removed by treatment with sodium methoxide in methanol yielding (XVI). Application of the standard synthetic route using (XVI) as starting material gave as anticipated 9-*l*-arabinofuranosido-2-methylthioadenine (XVII). Since it had previously been shown that replacement of the methylthio-group in 9-glycosido-2-methylthioadenines by hydrogen can be readily effected [13] by means of the elegant desulphurisation method of Mozingo [20] it is evident that the synthesis just described forms an exact model for the synthesis of adenosine. Such a synthesis is now being undertaken and there seems little reason to doubt its success if *d*-ribose proves analogous in behaviour to *l*-arabinose.

Before dealing with experiments bearing on the development of synthetic methods for the nucleotides, *i.e.*, methods of phosphorylation of nucleosides, a point of interest arising from the periodate method for determining lactol ring-structure in purine glycosides may be mentioned. It was observed [16] that yeast adenylic acid (adenosine 3′-phosphate) is unaffected by periodate. Muscle adenylic acid (adenosine 5′-phosphate) on the other hand takes up, like adenosine itself, one molar equivalent of periodate. This at once offered a method for determining unequivocally the structure of adenosine triphosphate, a substance which plays an important rôle in the transfer of phosphate in biological systems. The structure of adenosine triphosphate has hitherto been in some doubt. The titration evidence of Lohmann [21] (recently supported by that of Gulland [22]) clearly favoured the adenosine 5′-triphosphate structure (XVIII). Nevertheless other structures have been proposed by various workers [23] who claimed that it was possible, using certain enzyme preparations, to remove the acid-stable (5′) phosphate residue leaving the acid-labile residues intact; (XIX) may be taken as typical of such structures. It has now been shown that adenosine triphosphate is oxidised by periodate, one molar proportion of oxidant being consumed.[24] This we regard as conclusive proof that structure (XVIII) correctly represents adenosine triphosphate. It also follows that adenosine diphosphate is to be regarded as adenosine 5′-pyrophosphate and that, since cozymase yields adenosine diphosphate by hydrolytic cleavage, further support is given to structure (V) for the former substance.

Hitherto the synthesis of simple nucleotides by phosphorylation of nucleosides, using other than enzymic methods, has not been very practicable owing to the limitations of the methods used. Yeast and muscle adenylic acids have been prepared in very low yield by phosphorylation of adenosine with phosphoryl chloride in the presence of bases, with [25] or without [26] previous protection of other hydroxyl groups in the molecule, while treatment of 2′ : 3′-diacetyladenosine with diphenyl chlorophosphonate and subsequent removal of protecting groups again yielded very small amounts of muscle adenylic acid.[27] It seemed therefore that if our ends were to be achieved some other phosphorylation method would have to be devised. The requirements to be met by such a method would be (*a*) that it should proceed in good yield under mild conditions, (*b*) that no hydrolytic process should be involved which might damage sensitive glycosides, and (*c*) that it should be flexible enough to be capable of extension to the production of polyphosphoric esters.

The search for a convenient method of phosphorylation, fulfilling at any rate the first two requirements, has been pursued intermittently for many years by a considerable number of investigators without any really satisfactory result. Among the reagents which have been proposed are diphenyl chlorophosphonate,[27, 28]

phenyl dichlorophosphinate,[28, 29] anilinophosphonyl and dianilinophosphinyl chlorides,[30] ethyl metaphosphate,[31] and, recently, catechol-oxychlorophosphine.[32] We have made an extended study of this problem and have



selected for particular attention the use of dibenzyl chlorophosphonate.[33] This substance, which can be prepared by the action of chlorine on dibenzyl phosphite dissolved in an inert solvent [33] or by treatment of dibenzyl phosphate with thionyl chloride,[34] reacts readily with alcohols at room temperature in the presence of tertiary bases yielding esters of type (XX). From these products the benzyl groups can be removed smoothly and rapidly by catalytic hydrogenation. This method has been applied to the synthesis of muscle adenylic acid, which can be readily prepared in good yield by treatment of 2 : 3-*iso*propylideneadenosine with dibenzyl chlorophosphonate in pyridine followed by de-benzylation of the product and removal of the acetone residue with very dilute acid.[35]

The use of dibenzyl chlorophosphonate has a particular advantage in that removal of benzyl groups from the reactions by hydrogenolysis has been shown in a model experiment with dibenzyl *iso*amyl phosphate to proceed stepwise, *i.e.*, that partial hydrogenation yields benzyl *iso*amyl phosphate.[33] Since it has also been demonstrated in model experiments that, for example, dialkyl or diaryl chlorophosphonates react with silver dibenzyl phosphate to yield pyrophosphates, it is evident that we have here a potential method for the synthesis of polyphosphates and for the linkage of different molecules through polyphosphate residues. The realisation of this route in the case of nucleotides, in which technical difficulties are admittedly considerable, is at present one of our main preoccupations. Other routes to the same end which seem to offer promise of success I shall not deal with at this stage.

In this lecture I have attempted, however inadequately, to give a picture of the present position of a synthetic attack on the nucleotide problem. The problem is a very large one and it is clear that my colleagues and I have but touched on one aspect and it may well be that the difficulties in the way of our goal may be greater than we realise. Nevertheless we believe that the method of approach I have outlined may, coupled

with those of other chemists and biologists in the field, lead to a better understanding of the nature and rôle of the nucleotides in living matter.

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[2] *J.*, 1934, 1639; 1936, 765; 1938, 692.
[3] Levene and Tipson, *J. Biol. Chem.*, 1934, **104**, 385.
[4] *Idem, ibid.*, 1934, **105**, 419.
[5] *Ibid.*, 1937, **117**, 371.
[6] Fischer and Helferich, *Ber.*, 1914, **47**, 210.
[7] Baddiley, Lythgoe, McNeil, and Todd, *J.*, 1943, 383.
[8] Baddiley, Lythgoe, and Todd, *J.*, 1943, 571.
[9] Lythgoe, Todd, and Topham, *J.*, 1944, 315.
[10] Baddiley, Lythgoe, and Todd, *J.*, 1944, 318.
[11] Kenner, Lythgoe, and Todd, *J.*, 1944, 652.
[12] Kenner and Todd, *J.*, 1946, in press.
[13] Howard, Lythgoe, and Todd, *J.*, 1945, 556.
[14] Howard, Kenner, Lythgoe, and Todd, *J.*, 1946, in press.
[15] Baddiley, Kenner, Lythgoe, and Todd, *J.*, 1944, 657.
[16] Lythgoe and Todd, *J.*, 1944, 592.
[17] Davoll, Lythgoe, and Todd, *J.*, 1946, in press.
[18] Holland, Lythgoe, Smith, and Todd, *J.*, 1946, in press.
[19] Kenner, Lythgoe, and Todd, to be published.
[20] *J. Amer. Chem. Soc.*, 1943, **65**, 1013.
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[22] *J.*, 1945, 169.
[23] Satoh, *J. Biochem. Japan*, 1936, **21**, 19; Barrenscheen and Jachimowicz, *Biochem. Z.*, 1937, **292**, 350.
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[25] Levene and Tipson, *J. Biol. Chem.*, 1934, **106**, 113; 1935, **111**, 313; 1937, **121**, 131.
[26] Jachimowicz, *Biochem. Z.*, 1937, **292**, 356; Gulland and Hobday, *J.*, 1940, 746; Barker and Gulland, *J.*, 1942, 231.
[27] Bredereck, Berger, and Ehrenburg, *Ber.*, 1940, **73**, 269.
[28] Brigl and Müller, *ibid.*, 1939, **72**, 2121.
[29] Gulland and Hobday, *loc. cit.*
[30] Langheld, *Ber.*, 1910, **43**, 1857; 1911, **44**, 2076.
[31] Zetsche and Büttiker, *ibid.*, 1940, **73**, 47.
[32] Reich, *Nature*, 1946, **157**, 133.
[33] Atherton, Openshaw, and Todd, *J.*, 1945, 382.
[34] Deutsch and Fernō, *Nature*, 1945, **156**, 604.
[35] Baddiley and Todd, to be published shortly.

REPORT OF THE BUREAU OF ABSTRACTS FOR THE YEAR 1945.

1. *Introduction.*

No apology is needed for the length of the report for the year 1945. In the first place, the Bureau has been incorporated and, secondly, the importance of abstracting (always understood by those who sponsored the work during the past twenty-one years) is becoming more and more recognised. Government Departments and Industry have realised that abstracting is not only an important aid to the scientific worker, but is also a potent factor in the development of Trade. The members of the Board in common with many other scientists, both industrial and academic, realise that there is no division between " pure " and " applied " science. The constant survey of the vast field of science which comes within their purview stresses the conviction that the inextricable mingling of the paths of investigation defies any rigid classification into " pure " and " applied." Thus, studies on the nutritional value of a food may appear in the *Biochemical Journal* or in the *Journal of the Society of Chemical Industry*; in the one case it is regarded as " pure," and is therefore abstracted in *A Abstracts*, and in the second case as " applied," and appears in *B Abstracts*. Moreover, the synthesis of a compound reported in the *Journal of the Chemical Society* may form one part of an investigation, whilst a second part dealing with the applications of the compound may be reported in the *Journal of the Society of Chemical Industry*. To-day so many groups of scientists find it imperative to follow closely the progress of all sides of their subject that the purely artificial and arbitrary division of Abstracts and Indexes into two sections, so-called " pure " and " applied," involves some considerable extra labour and trouble. There is obviously a case for merging the A and B Abstracts, and this problem is receiving the attention of the Bureau.

2. *Incorporation.*

The negotiations with the Board of Trade about incorporation were more prolonged than had at first been expected, and it was not until June 22, 1945, that the Bureau became an incorporated body under the Companies Act 1929. This report accordingly covers the last six months of the existence of the Bureau in its original form as a joint committee and the first six months of its corporate existence as a separate entity. The Bureau wishes to record its appreciation of the labours of the Hon. Treasurer and the Solicitors in securing the completion of the incorporation and in the arduous task of preparing the Memorandum and Articles of Association.

The Bureau is now furnishing reports of the monthly meetings of the Board of Directors to the Supporting Societies, and also to the Chemical Council, and these reports are being published in *Chemistry and Industry*. The Bureau is informed that this has been much appreciated.

3. *Finance.*

Agreements have been entered into between the Bureau and the Chemical Society, the Society of Chemical Industry, the Physiological Society, and the Biochemical Society, providing for the payment of appropriate sums to the Bureau to cover current expenditure.

The Bureau has once again to record, with great appreciation, the receipt of a grant (£1500) from the Chemical Council in aid of the work of preparing the Abstracts for 1945. This generous gift is yet another token of the very practical interest which the Chemical Council has always evinced in the work of the Bureau.

4. *Directors and Members.*

The Board of Directors at the time of the incorporation consisted of the following : Dr. L. H. Lampitt (Chairman), Prof. B. A. McSwiney (Vice-Chairman), Mr. F. P. Dunn (Hon Treasurer), Mr. J. L. Baker, Dr. G. M. Bennett, Mr. H. W. Cremer, Dr. E. B. Hughes, Dr. L. A. Jordan, Dr. E. H. Rodd, Prof. S. Wright, Prof. F. G. Young. Prof. Young resigned his Directorship in July, and Dr. R. L. M. Synge has been appointed on nomination by the Biochemical Society to take his place. Two additional Directors were co-opted by the Board in August under Article 53—namely, Mr. E. J. Bowen and Dr. H. McCombie.

In addition to the Directors, the following have been appointed members of the Bureau by the Societies named : Chemical Society : Mr. R. P. Bell, Prof. H. V. A. Briscoe, Prof. G. A. R. Kon, Prof. W. Wardlaw; Society of Chemical Industry : Mr. E. B. Anderson, Dr. R. T. Colgate, Dr. H. McCombie, Prof. E. K. Rideal; Physiological Society : Prof. E. D. Adrian, Prof. H. P. Gilding; Biochemical Society : Dr. J. H. Bushill.

5. *Committees of the Bureau.*

The following is a list of the Committees appointed by the Bureau since its incorporation. (The Chairman, Vice-Chairman, and Hon. Treasurer are *ex officio* members of all Committees.)

Finance Committee:	Chairman, Vice-Chairman, Honorary Treasurer.
A I Abstracts	E. J. Bowen (Convener), H. J. T. Ellingham, W. Jevons, H. W. Thompson, A. J. E. Welch.
A II Abstracts	G. M. Bennett (Convener), G. A. R. Kon, H. McCombie, E. H. Rodd.
A III Abstracts	S. Wright (Convener), J. L. Baker, R. L. M. Synge.
B Abstracts	L. A. Jordan (Convener), A. L. Bacharach, H. W. Cremer, E. B. Hughes, F. M. Potter, V. Slater.
C Abstracts	E. B. Hughes (Convener), B. S. Cooper, R. C. Chirnside, E. J. King.
Indexing	E. H. Rodd (Convener), G. M. Bennett, C. L. Bird, E. J. Bowen, L. A. Jordan, G. A. R. Kon, J. H. Lane, C. Rimington, S. Wright.

6. *Publicity.*

The preparation of Brochure No. 1, entitled "The Bureau of Abstracts. What it is and what it offers," was almost completed by the end of 1945. Before final approval this document was carefully revised so that it should give a clear idea of the work and policy of the Bureau in an attractive form.

7. *Editorial Arrangements.*

From the time the Bureau was formed, the Secretary and Editor (Mr. T. F. Burton) had been responsible for editing the *Transactions* and *Annual Reports* of the Society of Chemical Industry. During the year the Society of Chemical Industry appointed a new Editor to be in charge of all its publications, and as from July 1st, Mr. Burton has devoted the whole of his time to the work of the Bureau.

Early in the year, Dr. E. E. Turner and Dr. H. Wren resigned their positions as Assistant Editors of Section A II, Organic Chemistry, which they had filled with conspicuous ability since the Bureau was formed in 1924. The Bureau desires to place on record its appreciation of their long and valuable services. The whole of the editing of Section A II has been placed in the hands of Dr. Harold Burton. A panel of four experienced organic chemists (Drs. F. E. King, C. W. Shoppee, J. C. Simpson, and L. F. Wiggins) are helping Dr. Burton in an advisory capacity with the abstracts of papers in certain branches of organic chemistry.

8. *Changes in Abstracts.*

A I. Realising that the classification of *Abstracts A I* (General, Physical, and Inorganic Chemistry) was not in complete harmony with recent progress in these branches of science, the Bureau adopted a revised classification which is believed to be more in keeping with modern ideas, and the Abstracts for 1946 will accordingly be subdivided under the following headings: I. Mathematical Theory. II. Sub-Atomics and Atomic Structure. III. Physical Properties and Molecular Structure of Single Substances. IV. Physical Properties and Molecular Structure of Solutions and Mixtures (not Electrochemical). V. Chemical Equilibria and Kinetics. VI. Electrochemical Equilibria and Kinetics. VII. Preparation of Inorganic Substances. VIII. General Reviews and Summaries. History. Lecture Experiments. IX. Geochemistry. (Full details of the classification are set in the Foreword of the 1946 Abstracts.)

A II. An important improvement has been made in this Section by each abstract beginning with an introductory paragraph describing the general nature and the results of the investigations recorded. It is believed that this feature has been much appreciated and has increased considerably the value of the abstracts of papers in Organic Chemistry.

The following changes in detail have been approved and will take effect in 1946: (i) physical constants in addition to m. p., b. p., and rotation will be quoted in future; (ii) aliphatic compounds with chains of more than 5 carbon atoms will be numbered (instead of giving Greek letters); (iii) the "delta" sign to denote unsaturated compounds will be abolished and the appropriate Greek letter or number will be inserted in the name of the compound immediately preceding the syllable which defines the unsaturated linking.

A III. Class XXV of this Section (Fungi. Micro-organisms. Immunology. Allergy) has been heavily overloaded and also contains a number of abstracts on widely varying aspects of these subjects. In the 1946 Abstracts, this Class will be divided into two: XXV, Biochemistry of Micro-organisms, including Fungi, and XXVI, Pathogenic Aspects of Micro-organisms. Immunology. Allergy. Parasitology. The remaining Classes will be renumbered accordingly.

In future the cross-references in A III to other sections of the Abstracts will be replaced by short abstracts.

Dr. F. G. Young is no longer able to assist in the editing of the Ductless Glands Section; this Section, and also that on Reproduction, are now in charge of Dr. J. M. Robson of Edinburgh.

B. The Bureau has been fortunate in securing a number of experts to serve on an Advisory Panel to assist the Editorial staff in the three Sections of *Abstracts B*. The constitution of the Panel is as follows:

Acids, Alkalis, Etc.	Dr. R. E. Slade
Agriculture	Sir Frank Engledow, F.R.S.
Building Materials	Dr. R. E. Stradling, F.R.S.
Ceramics	Dr. H. W. Webb
Chemical Engineering	Mr. J. A. Reavell
Fermentation	Prof. R. H. Hopkins
Fibres and Cellulose	Sir Robert Pickard, F.R.S.
Foods and Medicinal Products	Sir Jack Drummond, F.R.S.
Fuel and Gas	Sir Alfred Egerton, F.R.S.
Glass	Prof. W. E. S. Turner, F.R.S.
Insecticides	Sir Ian Heilbron, F.R.S.
Microbiology	Prof. H. Raistrick, F.R.S.
Metallurgy and Explosives	Dr. W. Cullen
Mineral Oils	Sir Frank Smith, F.R.S.
Non-Ferrous Metallurgy	Prof. C. H. Desch, F.R.S.
Oils and Fats	Prof. T. P. Hilditch, F.R.S.
Paints and Varnishes	Mr. C. A. F. Hastilow
Photography	Dr. H. Baines
Plastics	Mr. H. V. Potter
Rubber	Dr. D. F. Twiss
Sugars and Starches	Prof. W. N. Haworth, F.R.S.
Vegetable Products	Prof. A. C. Chibnall, F.R.S.

Already many valuable suggestions and comments have been received from these advisers, which will undoubtedly lead to improvement in all the Sections of Abstracts B.

C. This Section of the Abstracts (Analytical) continues to maintain its size and usefulness. In view of the large number of abstracts in class iii (Physiology, Biochemistry, etc.) and class iv (General Technique and Laboratory Apparatus) it has been decided that appropriate subheadings shall be inserted in these classes in the 1946 Abstracts.

9. *Indexing.*

The Bureau appreciates that the adequate indexing of the Abstracts is a matter of the utmost importance, since the value of the Abstracts as a work of reference depends very largely on the efficiency of the indexing. The Board has accordingly appointed a Committee to report on means whereby the indexing of the various Sections of the Abstracts may be improved. This Committee has been strengthened by the inclusion of Mr. C. L. Bird (nominated by the Society of Dyers and Colourists) and Mr. J. H. Lane (nominated by the Society of Public Analysts).

An important change in the 1946 Indexes, which it is believed will be approved by all organic chemists, is the inclusion of a Formula Index of organic compounds covering all the Sections of the Abstracts. This index will contain the formulæ of all new organic compounds, and also of those of which new properties or reactions are recorded, together with the appropriate Abstracts page reference.

10. *Statistics.*

Appendix 2 shows the number of abstracts which have appeared in the various Sections for 1945, with the figures for 1944 for comparison. It will be noted that the major increases are in A III and C, with smaller increases in A I and A II, whereas there is a small decrease in all Sections of B.

The increases in A I, A II, A III, and C are due chiefly to the inclusion of abstracts from a number of continental journals which were not previously available. The increases in numbers of abstracts, though small, are particularly gratifying, in view of the gradual decline which had been noted in recent years. It will be observed that the total number of pages of abstracts printed shows an increase of nearly 10%.

The Bureau realises that, with the ever-increasing developments in science and industry, the field covered by the Abstracts must increase, and consequently the list of journals abstracted must be continually expanded and new abstractors recruited. In order to obtain expert advice on these points, the Chemical Society and the Society of Chemical Industry have, at the request of the Bureau, asked their Local Sections and Groups to offer suggestions as to new journals which might usefully be added to the list of those already abstracted, and also to submit names of possible new abstractors. Valuable suggestions have already been received from these sources.

11. *Paper.*

It is not necessary to stress the difficulties which the Bureau, in common with all other Publishing Societies, has had owing to the shortage of paper. The Board, however, is pleased to be able to report

that the Paper Controller, taking into account the importance of the work carried out by the Bureau, has agreed to allot more paper for this work, and consequently the Bureau should be in a position to cope with the war-time journals which are now coming to hand.

12. *Offices.*

Since its formation in 1924 the Bureau has been housed in the offices of the Society of Chemical Industry, first at Finsbury Square, then at Clifton House (with an interlude at the Royal School of Mines owing to enemy action), and later at 56, Victoria Street. During the year the Bureau was informed by the Society of Chemical Industry that the whole of the Victoria Street offices would be required by the Society for immediate developments. At about the same time the Conjoint Chemical Office and the Indexing Department were faced with the necessity of removing from Burlington Gardens, and through the Chemical Society accommodation was found at 9—10 Savile Row, in which it was possible to house the whole of the staffs of the Conjoint Office and the Bureau and its indexing department. Although the present accommodation is inadequate and affords no facilities for expansion, the housing of all these departments in the same premises has proved a very great advantage, and it is hoped that extended accommodation may be available shortly.

13. *Appendix* 2.

The figures given in the appended Table show the number of abstracts and pages printed in each section during 1945, with comparative figures for 1944.

	1944.		1945.	
	No. of Abstracts.	Pages.	No. of Abstracts.	Pages.
A I	2472	148	2616	172
A II	1466	192	1515	210
A III	7554	428	8070	452
B I	4020	210	3798	202
B II	3124	192	3065	202
B III	2417	134	2262	132
C	2086	104	2739	150
	23,139	1408	24,065	1520

The above figures for *B* include abstracts of patents as follows: 1944, B I 2438, B II 2124, B III 548 (total 5107); 1945, B I 2198, B II 2001, B III 577 (total 4776).

THE BUREAU OF ABSTRACTS.

BALANCE SHEET, 31ST DECEMBER, 1945.

Liabilities.

A Company limited by Guarantee and not having a Share Capital.

	£ s. d.	£ s. d.
Abstracts A I and A II, B I, B II, and B III, and C.		
Sundry Creditors		3970 19 11
External Sales of Publications, prepaid		2284 3 2
General Reserve Account.		
As at 1st January, 1945	2000 0 0	
Add Contribution from The Chemical Council	1500 0 0	
		3500 0 0
		9755 3 1
Abstracts A III.		
Sundry Creditors	335 16 3	
External Sales of Publications—prepaid	814 14 0	
The Chemical Society for cost of Distribution—*less* Sales	269 10 8	
The Bureau of Abstracts	564 13 11	
Amount due to Abstracts A III Reserve Fund	900 0 0	
Excess of Assets over Liabilities as at 1st January, 1945 £296 2 3		
Add Excess of Income over Expenditure for year 66 16 10		
	362 19 1	
		3247 13 11
Abstracts A III Reserve Fund.		
Excess of Assets over Liabilities at 1st January, 1945	4131 11 6	
Add Amount transferred from Abstracts A III Account	900 0 0	
Excess of Income over Expenditure for year	63 10 1	
		5095 1 7
Collective Index Account.		
Sundry Creditors	12 7 2	
Excess of Assets over Liabilities at 1st January, 1945 £100 13 1		
Add Excess of Income over Expenditure for year 355 8 2		
	456 1 3	
		468 8 5
		£18,566 7 0

Assets.

	£ s. d.	£ s. d.
Abstracts A I and A II, B I, B II, and B III, and C.		
Sundry Debtors:		
The Chemical Society, balance at 1st January, 1945	268 5 11	
Net amount due for Sales of Abstracts—*less* payments for printing, etc.	1333 16 11	
	1602 2 10	
Add Excess of Expenditure over Income—Abstracts A I and A II	2464 13 7	
Proportion of cost of Abstracts C	531 18 9	
	4598 15 2	
Less Payments during year £268 5 11		
Do. do 1760 13 8		
	2028 19 7	
		2569 15 7
The Society of Chemical Industry, balance at 1st January, 1945	1372 9 1	
Add Net amount due for Externl Sales—*less* payments for printing, etc.	2147 0 2	
Excess of Expenditure over Income—Abstracts B I, B II, and B III	2626 15 11	
Proportion of Cost of Abstracts C	688 7 9	
	6834 12 11	
Less Payments during year	1900 0 0	
		4934 12 11
Abstracts A III: Amount due		564 13 11
Other Debtors		9 15 6
Cash at Bank	1075 0 3	
Petty Cash in hand	9 4 8	
		1084 4 11
Stock of Paper		592 0 3
		9755 3 1
Abstracts A III.		
Sundry Debtors:		
The Chemical Council £690 0 0		
The Biochemical Society 75 0 0		
	765 0 0	
Cash at Bank, on Deposit £1500 0 0		
Do. Current Account 982 13 11		
	2482 13 11	
		3247 13 11
Abstracts A III Reserve Fund.		
Investments:		
£700 3% Savings Bonds, 1955/65 £700 0 0		
£700 2½% National War Bonds, 1951/53 700 0 0		
£950 2½% National War Bonds, 1952/54 950 0 0		
£1700 1¼% Exchequer Bonds, 1950 1700 0 0		
	4050 0 0	
(Market value 31st December, 1945, £4074.)		
Amount due from Abstracts A III Account	900 0 0	
Cash at Bank	145 1 7	
		5095 1 7
Collective Index Account.		
Cash at Bank	466 16 7	
Cash in hand	1 11 10	
		468 8 5
		£18,566 7 0

L. H. LAMPITT, *Chairman.*
F. P. DUNN, *Treasurer.*

AUDITORS REPORT TO THE MEMBERS.

We have audited the above Balance Sheet made up to 31st December, 1945, and the accompanying Accounts of the Bureau, with the Books and vouchers submitted to us, and have received all the information and explanations we have required. In our opinion the Balance Sheet is properly drawn up so as to exhibit a true and correct view of the state of the Bureau's affairs according to the best of our information and the explanations given to us and as shown by the books of the Bureau.

FINSBURY CIRCUS HOUSE,
LONDON, E.C.2.

W. B. KEEN & CO.,
Chartered Accountants.

INCOME AND EXPENDITURE ACCOUNTS (INCLUDING UNINCORPORATED BUREAU) FOR THE YEAR ENDED 31ST DECEMBER, 1945.

ABSTRACTS A I AND A II

our information and the explanations given to us and as shown by the books of the Bureau.

FENSBURY CIRCUS HOUSE,
LONDON, E.C.2.

W. B. KEEN & CO.,
Chartered Accountants.

INCOME AND EXPENDITURE ACCOUNTS (INCLUDING UNINCORPORATED BUREAU) FOR THE YEAR ENDED 31ST DECEMBER, 1945.

ABSTRACTS A I AND A II.

1944	*Expenditure.*		1945		1944	*Income.*		1945	
£ s. d.		£ s. d.	£ s. d.		£ s. d.		s. d.	£ s. d.	
	To Abstracts A I:				2652 1 11	By External Sales		2866 5 2	
1607 13 1	Publishing, etc.		1990 7 4		56 2 8	„ Net Revenue from Advertisements		52 2 2	
	„ Index:					„ Transfer to Balance Sheet (the balance of expenditure on			
301 3 11	Publishing, etc.		314 16 3		1906 19 11	publications)		2464 13 7	
213 19 2	„ Share of Overhead Expenses, C.S.		157 8 1						
51 13 4	„ Do. do. S.C.I., 1944	50 13 4							
	1945	33 15 7							
			84 8 11						
	„ Abstracts A II:								
1823 15 8	Publishing, etc.		2166 16 10						
	„ Index:								
351 6 10	Publishing, etc.		427 6 6						
213 19 2	„ Share of Overhead Expenses, C.S.		157 8 1						
51 13 4	„ Do. do. S.C.I., 1944	50 13 4							
	1945	33 15 7							
			84 8 11						
£4615 4 6			£5383 0 11		£4615 4 6			£5383 0 11	

ABSTRACTS A III.

£ s. d.		£ s. d.	£ s. d.	£ s. d.	£ s. d.		£ s. d.	£ s. d.	
	To Abstracts A III:			3168 12 5		By External Sales		3061 3 3	
3066 12 8	Publishing, etc.		3590 11 3	6 1 9		„ Interest on Deposit		6 18 8	
	„ Index:					„ Contributions:			
869 2 11	Publishing, etc.		915 14 2		1500 0 0	The Chemical Society	1500 0 0		
213 19 1	„ Share of Overhead Expenses, C.S.		157 8 1		400 0 0	The Physiological Society	400 0 0		
51 13 4	„ Do. do. S.C.I., 1944	50 13 4			300 0 0	The Biochemical Society	300 0 0		
	1945	33 15 6			100 0 0	The Anatomical Society	100 0 0		
			84 8 10		50 0 0	The Society for Experimental Biology ...	50 0 0		
173 11 9	„ Contribution to Abstracts C, proportion of cost		344 3 11		466 0 0	The Chemical Council	690 0 0		
— — —	„ Do. to Quinquennial Index		75 0 0		75 0 0	The Society of Chemical Industry	— — —		
1700 0 0	„ Transfer to Reserve Fund		900 0 0	2891 0 0				3040 0 0	
	„ Excess of Income over Expenditure carried to Balance			28 1 5		„ Net Revenue from Advertisements		26 1 2	
18 15 10	Sheet		66 16 10						
£6093 15 7			£6134 3 1	£6093 15 7				£6134 3 1	

ABSTRACTS B I, B II, AND B III.

1944	*Expenditure.*		1945		1944	*Income.*		1945	
£ s. d.		£ s. d.	£ s. d.		£ s. d.			£ s. d.	
	To Abstracts B I:				3056 17 5	By External Sales		4145 9 6	
1840 17 9	Publishing, etc.		1962 13 6		2 11 4	„ Share of Fees and Sundry Sales		— — —	
	„ Index:				3298 17 8	„ Transfer to Balance Sheet (the balance of expenditure on publications)		2626 15 11	
455 4 4	Publishing, etc.		435 18 10						
111 13 4	„ Share of Overhead Expenses		62 9 5						
	„ Abstracts B II:								
1760 13 10	Publishing, etc.		2005 2 6						
	„ Index:								
372 12 1	Publishing, etc.		435 18 8						
111 13 4	„ Share of Overhead Expenses		62 9 4						
	„ Abstracts B III:								
1314 9 8	Publishing, etc.		1454 7 8						
	„ Index:								
279 8 9	Publishing, etc.		290 16 2						
111 13 4	„ Share of Overhead Expenses		62 9 4						
£6358 6 5			£6772 5 5		£6358 6 5			£6772 5 5	

Income and Expenditure Accounts (including unincorporated Bureau) for the year ended 31st December, 1945.

Abstracts C.

1944 £ s. d.	*Expenditure.*	1945 £ s. d.	1944 £ s. d.	£ s. d.	*Income.*	£ s. d.	1945 £ s. d.
	To Abstracts C:		45 14 0		By External Sales		78 19 3
834 15 7	Publishing, etc.	1496 0 8	— — —		„ Net Revenue from Advertisements		45 0 0
— — —	„ Index:				„ Transfer to Balance Sheet:		
	Publishing, etc.	192 9 0		268 5 11	Abstracts A I and A II	531 18 9	
				347 3 11	Abstracts B I, B II, and B III	688 7 9	
				173 11 9	Transfer to Abstracts A III	344 3 11	
			789 1 7				1564 10 5
£834 15 7		£1688 9 8	£834 15 7				£1688 9 8

Abstracts A III Reserve Fund.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
47 17 0	To Excess of Income over Expenditure carried to Balance Sheet	63 10 1	33 17 0	By Dividends on Investments	44 14 5
			14 0 0	„ Income Tax recovered	18 15 8
£47 17 0		£63 10 1	£47 17 0		£63 10 1

Collective Index Account.

£ s. d.		£ s. d.	£ s. d.		£ s. d.	£ s. d.
— — —	To Salaries	329 16 3	— — —	By Contributions:		
— — —	„ Despatch	9 11 6	— — —	The Chemical Society	175 0 0	
— — —	„ Miscellaneous	8 15 3	— — —	The Society of Chemical Industry	200 0 0	
— — —	„ Excess of Income over Expenditure carried to Balance Sheet	355 8 2	— — —	Abstracts A III	75 0 0	
						450 0 0
			— — —	„ Sales, Quinquennial Index	199 9 0	
			— — —	„ Sales, Decennial Index	54 2 2	
						253 11 2
£— — —		£703 11 2	£— — —			£703 11 2

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